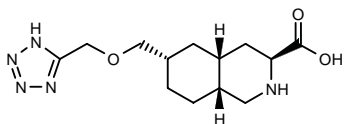


ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

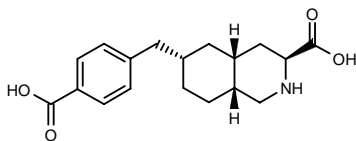
269986

[3*S*-(3 α ,4 α ,6 β ,8 α)]-6-(1*H*-Tetrazol-5-ylmethoxymethyl)-decahydroisoquinoline-3-carboxylic acid



C13 H21 N5 O3; Mol wt: 295.3409

ACTION – Analgesic agent, a selective kainate GluR5 receptor antagonist ($K_i = 5823$ nM in HEK293 cells transfected with the human GluR5 receptor) proven active in several animal models of pain; it was active in the tail-flick test in mice following s.c. administration of 3-30 mg/kg and in cynomolgus monkeys following oral doses of 0.03-3 mg/kg, as well as in the acetic acid-induced writhing test in mice. Another specifically claimed compound is:



269987: C18 H23 N O4

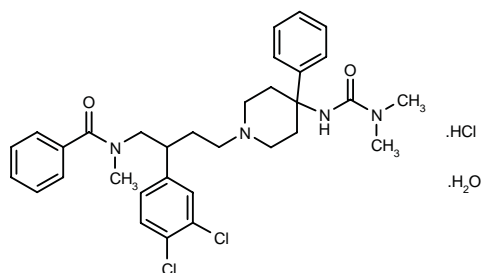
SOURCE – Lilly.

REFERENCES

1. Bleakman, D. et al. (Eli Lilly and Company) *Pharmacological agents*. WO 9845270.

270190

(–)-*N*-[2-(3,4-Dichlorophenyl)-4-[4-(3,3-dimethylureido)-4-phenylpiperidin-1-yl]butyl]-*N*-methylbenzamide hydrochloride hydrate



C32 H38 Cl2 N4 O2 . HCl . H2O; Mol wt: 636.0599

ACTION – Tachykinin receptor antagonist reported to bind with high affinity to NK₁, NK₂ and NK₃ receptors, with potential in the treatment of pain, inflammation and immunological, gastrointestinal, cardiovascular and CNS disorders. A specifically claimed compound from a series of piperidine derivatives.

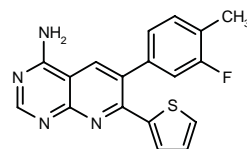
SOURCE – Sanofi.

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1. Chabert, N. et al. (Sanofi) *Piperidine derivs., process for obtaining them and pharmaceutical compsns. containing them*. US 5830906.

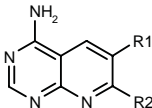
270383

6-(3-Fluoro-4-methylphenyl)-7-(2-thienyl)pyrido[2,3-*d*]-pyrimidin-4-amine



C18 H13 F N4 S; Mol wt: 336.3927

ACTION – Agent for the treatment of pain, cerebral and myocardial ischemia, angina, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, rheumatoid arthritis, gastrointestinal dysfunction, diabetes and sepsis, as well as for use in coronary artery bypass graft (CABG) surgery and percutaneous transluminal angioplasty (PTCA), that acts by inhibiting adenosine kinase (IC₅₀ = 5 nM using human neuroblastoma IMR-32 cells as the source of the enzyme). Compound was active in the hot-plate test in mice, with significant antinociceptive activity at a dose of 30 mg/kg i.p. Other representative compounds within this series of specifically claimed 6,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidine derivatives include the following:



Compound	R1	R2	Formula
270384	Bu	2-thienyl	C ₁₅ H ₁₆ N ₄ S
270385	C ₅ H ₁₁	4-N(Me)2-Ph	C ₂₀ H ₂₅ N ₅
270386	3-MeO-PhCH ₂	4-N(Me)2-Ph	C ₂₃ H ₂₃ N ₅ O
270387	3-Br-4-MeO-Ph	2-thienyl	C ₁₈ H ₁₃ BrN ₄ OS

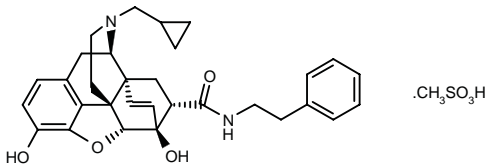
SOURCE – Abbott.

REFERENCES

1. Bhagwat, S.S. et al. (Abbott Laboratories Inc.) 6,7-Disubst. -4-aminopyrido[2,3-*d*]pyrimidine cpds. WO 9846603.

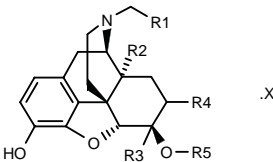
270433

17-(Cyclopropylmethyl)-4,5α-epoxy-3,6β-dihydroxy-*N*-(2-phenylethyl)-6α,14α-vinylenomorphinan-7α-carboxamide methanesulfonate



C31 H34 N2 O4 . C H4 O3 S; Mol wt: 594.7252

ACTION – Analgesic agent, an ε-opioid receptor agonist, as demonstrated by inhibition of electrically stimulated contractions in isolated rat vas deferens (32% inhibition at 2.5 μM), whose activity was assayed in mice in the acetic acid-induced writhing test (ED₅₀ = 238.8 μg/kg s.c.) and in the hot-plate test (ED₅₀ = 2.64 mg/kg s.c.). A representative compound from a series of morphinan derivatives with agonist or antagonist activity at ε-opioid receptors, wherein the following are also included:



Compound	R1	R2,R3	R4	R5	X	Formula
270434	cyclopropyl	-CH=CH-	α-CON(Me)-CH ₂ CH ₂ Ph	H	MeSO ₃ H	C ₃₂ H ₃₆ N ₂ O ₄ .CH ₄ O ₃ S
270435	cyclopropyl	-(CH ₂) ₂ -	α-CON(Me)-CH ₂ CH ₂ Ph	H	MeSO ₃ H	C ₃₂ H ₃₈ N ₂ O ₄ .CH ₄ O ₃ S
270436	CH ₂ Ph	-CH=CH-	α-CON(Me)-CH ₂ CH ₂ Ph	H	MeSO ₃ H	C ₃₆ H ₃₈ N ₂ O ₄ .CH ₄ O ₃ S
270437	cyclopropyl	-CH=CH-	α-CONH-CH ₂ Ph	H	MeSO ₃ H	C ₃₀ H ₃₂ N ₂ O ₄ .CH ₄ O ₃ S
270438	cyclopropyl	-CH=CH-	β-CONH-CH ₂ CH ₂ Ph	H		C ₃₁ H ₃₄ N ₂ O ₄
270439	cyclopropyl	-CH=CH-	α-CONH(CH ₂) ₄ Ph	H	MeSO ₃ H	C ₃₃ H ₃₈ N ₂ O ₄ .CH ₄ O ₃ S
270440	cyclopropyl	-CH=CH-	β-CONH(CH ₂) ₄ Ph	H		C ₃₃ H ₃₈ N ₂ O ₄
270441	cyclopropyl	-CH=CH-	β-NHCO(CH ₂) ₄ Ph	Me	MeSO ₃ H	C ₃₄ H ₄₀ N ₂ O ₄ .CH ₄ O ₃ S
270442	cyclopropyl	-CH=CH-	α-NHCO(CH ₂) ₄ Ph	Me	MeSO ₃ H	C ₃₄ H ₄₀ N ₂ O ₄ .CH ₄ O ₃ S

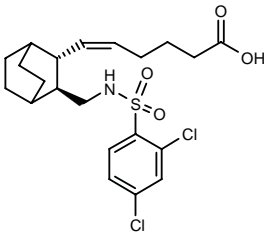
SOURCE – Toray.

REFERENCES

1. Nagase, H. et al. (Toray Industries, Inc.) Morphinane derivs. and medicinal use thereof. WO 9843978.

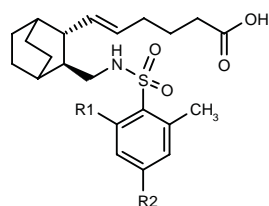
270562

(*Z*)-6-[(2*R*,3*S*)-3-(2,4-Dichlorophenylsulfonamidomethyl)bicyclo[2.2.2]oct-2-yl]-5-hexenoic acid

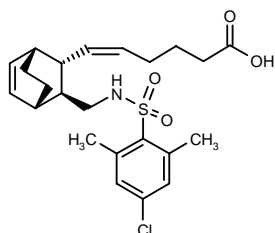


C21 H27 Cl2 N O4 S; Mol wt: 460.4193

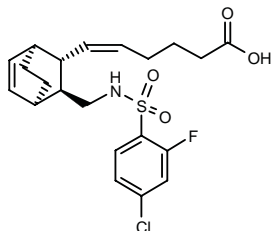
ACTION – Potent PGE₂ antagonist with high selectivity for EP₁ receptors (K_i = 0.5 nM) relative to EP₃ receptors (K_i = 0.12 μM), potentially useful as an analgesic and antipyretic agent and for use in the treatment or prevention of pollakiuria. Within this series of benzenesulfonamide derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
270563	H	Cl	Z	C ₂₂ H ₃₀ ClNO ₄ S
270564	H	Br	Z	C ₂₂ H ₃₀ BrNO ₄ S
270565	Cl	Cl	Z	C ₂₂ H ₂₈ Cl ₂ NO ₄ S
270566	H	Cl	E	C ₂₂ H ₃₀ ClNO ₄ S



270567: C₂₃ H₃₀ Cl N O₄ S



270568: C₂₁ H₂₅ Cl F N O₄ S

SOURCE – Ono.

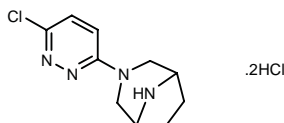
REFERENCES

1. Ohuchida, S. et al. (Ono Pharmaceutical Co., Ltd.) *Benzenesulfonamide cpds.* EP 878465.

DBO-83

257627

3-Chloro-6-(3,8-diazabicyclo[3.2.1]oct-3-yl)pyridazine dihydrochloride



C₁₀ H₁₃ Cl N₄ . 2HCl; Mol wt: 297.6155

ACTION – Nicotinic acetylcholine receptor (nAChR) agonist that binds with high affinity to the central $\alpha 4\beta 2$ nAChR subtype ($K_i = 4.1 \pm 0.21$ nM for inhibition of [³H]-cytisine binding in rat cerebral cortical membranes) and acts as a full agonist at both ganglionic and central nAChR subtypes ($EC_{50} = 12.2 \pm 1.9$ and 24.0 ± 3.1 μ M, respectively; intrinsic activity relative to 100 μ M (–)nicotine = 122.6 and 164.7%, respectively), whereas it showed no activity at neuromuscular subtypes ($EC_{50} > 1000$ μ M). *In vivo*, compound exhibited significant antinociceptive activity in the mouse hot-plate and

abdominal constriction tests and the rat paw-pressure test, effects which were prevented by the nicotine antagonist mecamylamine but not the opioid antagonist naloxone. At pharmacological doses it did not impair motor coordination or spontaneous motility in mice. DBO-83 also proved effective against amnesia induced by a variety of pharmacological agents in mice including scopolamine, mecamylamine and baclofen.

SOURCES – Università degli Studi di Firenze, Firenze (IT); Università degli Studi di Milano, Milano (IT).

REFERENCES

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2. Caldari, B. et al. *Antiamnesic activity of the novel nicotinic agonist DBO-83.* Soc Neurosci Abst 1998, 24(Part 1): Abst 76.4.

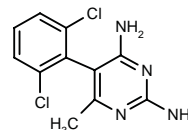
3. Ghelardini, C. et al. *Antiamnesic activity of the nicotinic agonist DBO-83 in mice.* Drug Dev Res 1998, 45(2): 45.

4. Ghelardini, C. et al. *Antinociceptive profile of the new nicotinic agonist DBO-83.* Drug Dev Res 1997, 40(3): 251.

GW-273227

267796

5-(5,6-Dichlorophenyl)-6-methylpyrimidine-2,4-diamine



C₁₁ H₁₀ Cl₂ N₄; Mol wt: 269.1340

ACTION – Sodium channel inhibitor related to lamotrigine and BW-1003C87, with potential in the treatment of pain.

SOURCE – Glaxo Wellcome.

REFERENCES

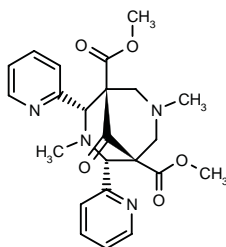
1. Miller, A.A. et al. (Glaxo Wellcome plc) *Pharmacologically active CNS cpds.* AU 8945964, EP 372934, EP 713703, EP 715851, EP 727212, EP 727213, EP 727214, JP 90202876, US 5587380, US 5597828, US 5635507, US 5684005.

2. Shah, G.P. et al. *Sodium channel inhibitors 2: Structure activity relationships of the lamotrigine series.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.192.

HZ2

269257

(1*R*,2*S*,4*R*,5*S*)-3,7-Dimethyl-9-oxo-2,4-di(2-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylic acid dimethyl ester



C23 H26 N4 O5; Mol wt: 438.4814

ACTION – Analgesic agent, a potent and selective κ -opioid receptor agonist ($K_i = 15$ nM against [3 H]-CI-977 binding in rat brain membrane preparations; $K_i > 1$ and > 10 μ M, respectively, for μ - and δ -opioid receptors). In guinea pig ileum and rabbit vas deferens, it inhibited electrically evoked contractions with IC_{50} values of 0.59 μ mol/l and 8.23 μ mol/l, respectively; the effect in rabbit vas deferens was completely inhibited by the selective κ -opioid receptor antagonist norbinaltorphine. *In vivo*, compound produced dose-dependent antinociceptive effects against thermal (tail-flick, hot-plate), chemical (phenylquinone-induced writhing) or electrical (tooth pulp stimulation) stimuli in rats, mice and rabbits, with a potency comparable to morphine. In mice, the antinociceptive ED_{50} values after i.v. administration ranged from 0.33 mg/kg (in the phenylquinone writhing test) to 3.18 mg/kg (in the hot-plate test), and in the tail-flick test the compound showed a potent ($ED_{50} = 2.23$ mg/kg i.v.) and prolonged (over 7 h) analgesic effect. In rats, the antinociceptive effect appeared to be lower than in mice after both i.v. and p.o. administration; in the rabbit tooth pulp stimulation test, it showed strong analgesic activity ($ED_{50} = 0.64$ mg/kg i.v.). Compound had high oral bioavailability in both mice and rats. HZ2 also displayed analgesic activity in inflammatory and persistent pain at higher doses. Although it is not associated with morphine-like physical dependence or respiratory depression, it produces diuresis and sedation.

SOURCE – Grünenthal.

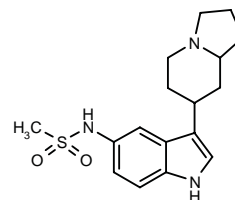
REFERENCES

1. Brandt, W. et al. Search for the pharmacophore in κ -agonistic diazabicyclo[3.3.1]nonan-9-one-1,5-diester and arylacetamides. Arch Pharm 1996, 329(6): 311.
2. Comba, P. et al. The design of a new type of very rigid tetradentate ligand. J Chem Soc Dalton Trans 1997, 347.
3. Haller, R. and Unholzer, H. Stereochemistry of 3-oxa-7-aza- and 3,7-diazabicyclo[3.3.1]nonan-9-ones. Arch Pharm 1972, 305(11): 855.
4. Kögel, B. et al. HZ2, a selective kappa-opioid agonist. CNS Drug Rev 1998, 4(1): 54.
5. Samhammer, A. et al. Reductions of 3,7-diazabicyclo[3.3.1]nonan-9-ones and corresponding 1,3-diazaadamantan-6-ones. Arch Pharm 1989, 322(9): 545.
6. Samhammer, A. et al. Synthesis, stereochemistry and analgesic activity of 3,7-diazabicyclo[3.3.1]nonan-9-ones and 1,3-diazaadamantan-6-ones. Arch Pharm 1989, 322(9): 551.

ANTIMIGRAINE DRUGS

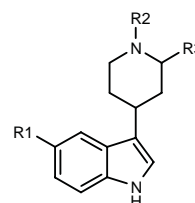
270041

N-[3-(Perhydroindolizin-7-yl)-1*H*-indol-5-yl]methanesulfonamide

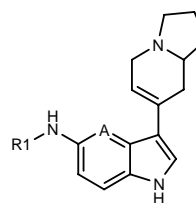


C17 H23 N3 O2 S; Mol wt: 333.4537

ACTION – Antimigraine agent, a selective 5-HT_{1F} receptor agonist able to inhibit protein extravasation induced by stimulation of the trigeminal ganglia. Other representative compounds within this series of substituted hetero-aromatic derivatives include the following:



Compound	R1	R2,R3	Formula
270042	Cl	-(CH2)3-	C ₁₆ H ₁₉ ClN ₂
270043	4-F-PhCONH	-(CH2)3-	C ₂₃ H ₂₄ FN ₃ O
270044	4-F-PhCONH	-(CH2)4-	C ₂₄ H ₂₆ FN ₃ O
270046	OH	-(CH2)3-	C ₁₆ H ₂₀ N ₂ O
270047	F	-(CH2)3-	C ₁₆ H ₁₉ FN ₂
270048	NHCONHMe	-(CH2)3-	C ₁₈ H ₂₄ N ₄ O



Compound	R1	A	Formula
270045	SO ₂ Me	CH	C ₁₇ H ₂₁ N ₃ O ₂ S
270049	4-F-PhCO	N	C ₂₂ H ₂₁ FN ₄ O
270050	Ac	N	C ₁₇ H ₂₀ N ₄ O

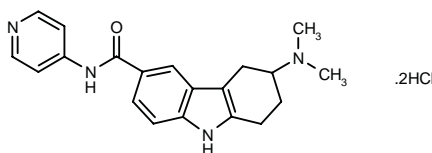
SOURCE – Lilly.

REFERENCES

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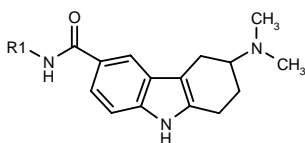
270667

3-(Dimethylamino)-*N*-(4-pyridinyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxamide dihydrochloride

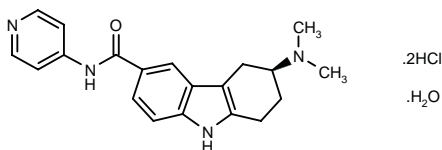


C₂₀ H₂₂ N₄ O . 2HCl; Mol wt: 407.3426

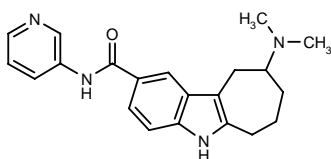
ACTION – Antimigraine agent, a selective 5-HT_{1F} receptor agonist reported to inhibit neuronal protein extravasation due to stimulation of the trigeminal ganglia. A representative compound from a series of carbazole carboxamides, wherein the following are also included:



Compound	R1	Formula
270669	cyclopropyl	C ₁₈ H ₂₃ N ₃ O
270670	cyclopentyl	C ₂₀ H ₂₇ N ₃ O
270671	5-(CO ₂ Me)-2-furyl	C ₂₁ H ₂₃ N ₃ O ₄
270672	2-Cl-3-Pyr	C ₂₀ H ₂₁ ClN ₄ O
270673	6-MeO-3-Pyr	C ₂₁ H ₂₄ N ₄ O ₂



270668: C₂₀ H₂₂ N₄ O . 2HCl . H₂O



270674: C₂₁ H₂₄ N₄ O

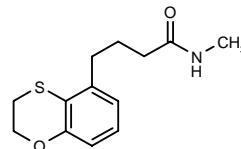
SOURCE – Lilly.

REFERENCES

1. Flaugh, M.E. (Eli Lilly and Company) *Carbazol-carboxamides as 5-HT_{1F} agonists*. EP 882726, WO 9855115.

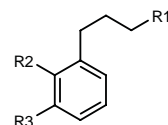
PSYCHOPHARMACOLOGIC DRUGS**TREATMENT OF SLEEP DISORDERS****270234**

4-(2,3-Dihydro-1,4-benzoxathiin-5-yl)-*N*-methylbutyr-
amide



C₁₃ H₁₇ N O₂ S; Mol wt: 251.3483

ACTION – Agent with strong affinity for melatonin receptors particularly useful for the treatment of seasonal depression, sleep disorders, cardiovascular pathologies, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic and antiarrhythmic activity, and to have a powerful effect on circadian rhythms via the melatonergic system in animal models. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2,R3	Formula
270235	CONHEt	-SCH ₂ CH ₂ O-	C ₁₄ H ₁₉ NO ₂ S
270236	NHCOPr	-OCH=CHO-	C ₁₅ H ₁₉ NO ₃
270237	CONHMe	-OCH ₂ CH ₂ O-	C ₁₃ H ₁₇ NO ₃

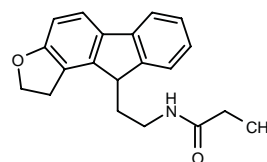
SOURCE – ADIR.

REFERENCES

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270869

N-[2-(2,10-Dihydro-1*H*-fluoreno[2,1-*b*]furan-10-yl)ethyl]-
propionamide

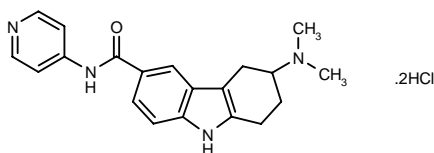


C₂₀ H₂₁ N O₂; Mol wt: 307.3909

ACTION – Melatonin agonist (IC₅₀ < 25 nM against 2-[¹²⁵I]-iodomelatonin binding to human melatonin mt₁ [ML_{1A}] receptors expressed in NIH 3T3 cells), potentially useful for the treatment of sleep and circadian rhythm disorders. Another specifically claimed compound from this series of polycyclic ethyl alkylamide derivatives is:

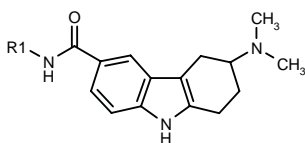
270667

3-(Dimethylamino)-*N*-(4-pyridinyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxamide dihydrochloride

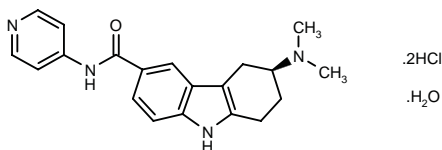


C₂₀ H₂₂ N₄ O . 2HCl; Mol wt: 407.3426

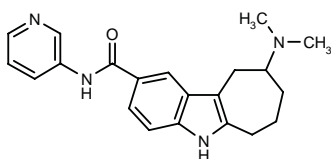
ACTION – Antimigraine agent, a selective 5-HT_{1F} receptor agonist reported to inhibit neuronal protein extravasation due to stimulation of the trigeminal ganglia. A representative compound from a series of carbazole carboxamides, wherein the following are also included:



Compound	R1	Formula
270669	cyclopropyl	C ₁₈ H ₂₃ N ₃ O
270670	cyclopentyl	C ₂₀ H ₂₇ N ₃ O
270671	5-(CO ₂ Me)-2-furyl	C ₂₁ H ₂₃ N ₃ O ₄
270672	2-Cl-3-Pyr	C ₂₀ H ₂₁ ClN ₄ O
270673	6-MeO-3-Pyr	C ₂₁ H ₂₄ N ₄ O ₂



270668: C₂₀ H₂₂ N₄ O . 2HCl . H₂O



270674: C₂₁ H₂₄ N₄ O

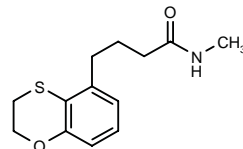
SOURCE – Lilly.

REFERENCES

1. Flaugh, M.E. (Eli Lilly and Company) *Carbazol-carboxamides as 5-HT_{1F} agonists*. EP 882726, WO 9855115.

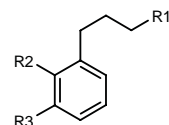
PSYCHOPHARMACOLOGIC DRUGS**TREATMENT OF SLEEP DISORDERS****270234**

4-(2,3-Dihydro-1,4-benzoxathiin-5-yl)-*N*-methylbutyr-
amide



C₁₃ H₁₇ N O₂ S; Mol wt: 251.3483

ACTION – Agent with strong affinity for melatonin receptors particularly useful for the treatment of seasonal depression, sleep disorders, cardiovascular pathologies, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic and antiarrhythmic activity, and to have a powerful effect on circadian rhythms via the melatonergic system in animal models. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2,R3	Formula
270235	CONHEt	-SCH ₂ CH ₂ O-	C ₁₄ H ₁₉ NO ₂ S
270236	NHCOPr	-OCH=CHO-	C ₁₅ H ₁₉ NO ₃
270237	CONHMe	-OCH ₂ CH ₂ O-	C ₁₃ H ₁₇ NO ₃

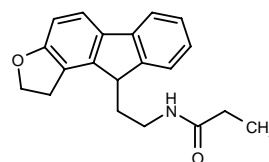
SOURCE – ADIR.

REFERENCES

1. Guillaumet, G. et al. (ADIR et Cie.) *Heterocyclic cpds., process for their preparation and pharmaceutical compsns. containing them*. EP 873993, JP 98298178.

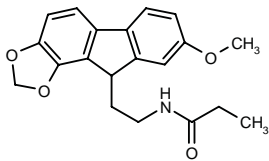
270869

N-[2-(2,10-Dihydro-1*H*-fluoreno[2,1-*b*]furan-10-yl)ethyl]-
propionamide



C₂₀ H₂₁ N O₂; Mol wt: 307.3909

ACTION – Melatonin agonist (IC₅₀ < 25 nM against 2-[¹²⁵I]-iodomelatonin binding to human melatonin mt₁ [ML_{1A}] receptors expressed in NIH 3T3 cells), potentially useful for the treatment of sleep and circadian rhythm disorders. Another specifically claimed heterocyclic compounds include the following:



270871: C20 H21 N O4

SOURCE – Bristol-Myers Squibb.

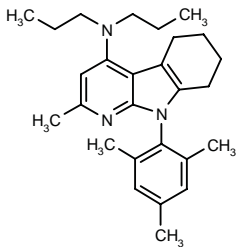
REFERENCES

1. Epperson, J. et al. (Bristol-Myers Squibb Co.) *Polycyclic ethyl alkylamide melatonergic agents*. WO 9838991.

ANXIOLYTICS

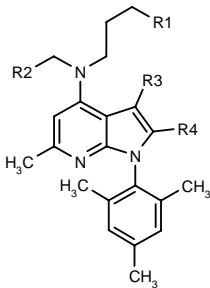
270051

N-[2-Methyl-9-(2,4,6-trimethylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-4-yl]-*N,N*-dipropylamine

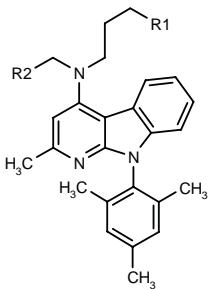


C27 H37 N3; Mol wt: 403.6103

ACTION – Agent for the treatment of stress-related disorders, depression, headache and anxiety that selectively binds to the corticotropin-releasing factor CRF₁ receptor, giving an IC₅₀ value of 0.011 μM. Other specifically claimed pyrrolopyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
270052	H	cyclopropyl	-(CH2)4-		C ₂₈ H ₃₇ N ₃
270054	Me	Me	-(CH2)4-		C ₂₇ H ₃₇ N ₃
270057	H	Et	Me	Me	C ₂₅ H ₃₅ N ₃
270058	H	cyclopropyl	Me	Me	C ₂₆ H ₃₅ N ₃
270059	Me	Me	Me	Me	C ₂₅ H ₃₅ N ₃



Compound	R1	R2	Formula
270053	H	cyclopropyl	C ₂₈ H ₃₃ N ₃
270055	H	Et	C ₂₇ H ₃₃ N ₃
270056	Me	Me	C ₂₇ H ₃₃ N ₃

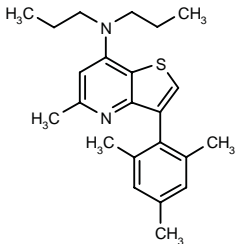
SOURCE – Neurogen.

REFERENCES

1. Horvath, R.F. and Hutchinson, A. (Neurogen Corp.) *Certain pyrrolopyridine derivs.; novel CRF1 specific ligands*. WO 9845295.

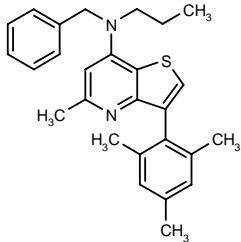
270712

N-[5-Methyl-3-(2,4,6-trimethylphenyl)thieno[3,2-*b*]pyridin-7-yl]-*N,N*-dipropylamine



C23 H30 N2 S; Mol wt: 366.5700

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist with potential in the treatment of disorders related to CRF hypersecretion such as anxiety, depression, eating disorders, stress-induced immune suppression, stroke, Cushing's disease, infantile spasms, epilepsy, seizures or inflammation. Another specifically claimed compound from this series of thienopyridines is:



270713: C27 H30 N2 S

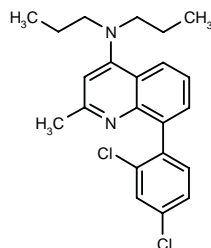
SOURCES – Janssen; Neurocrine Biosciences.

REFERENCES

1. Webb, T.R. and McCarthy, J.R. (Janssen Pharmaceutica NV; Neurocrine Biosciences Inc.) *CRF antagonistic thiophenopyridines*. WO 9847903.

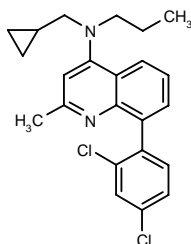
270714

N-[8-(2,4-Dichlorophenyl)-2-methyl-4-quinoliny]-*N,N*-dipropylamine



C22 H24 Cl2 N2; Mol wt: 387.3516

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist with potential in the treatment of disorders related to CRF hypersecretion such as anxiety, depression, eating disorders, stress-induced immune suppression, stroke, Cushing's disease, infantile spasms, epilepsy, seizures or inflammation. Another specifically claimed compound from this series of quinolines and quinazolines is:



270715: C23 H24 Cl2 N2

SOURCES – Janssen; Neurocrine Biosciences.

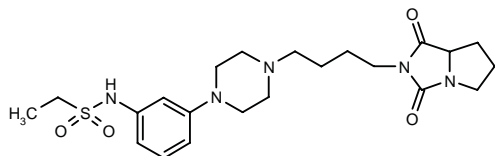
REFERENCES

- Huang, C. et al. (Janssen Pharmaceutica NV; Neurocrine Biosciences Inc.) *CRF antagonistic quino- and quinazolines*. WO 9847874.

EF-7412

267680

N-[3-[4-[4-(1,3-Dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-2-yl)butyl]piperazin-1-yl]phenyl]ethanesulfonamide



C22 H33 N5 O4 S; Mol wt: 463.5997

ACTION – Potent 5-HT_{1A} and dopamine D₂ receptor antagonist that binds with high affinity to both receptors (K_i = 27.3 and 22.2 nM, respectively) but shows low affinity (K_i > 1000) for 5-HT_{2A}, 5-HT₃ and 5-HT₄ receptors and α₁-adrenoceptors. *In vivo*, compound exhibited pre- and postsynaptic 5-HT_{1A} receptor-antagonist activity, but was devoid of anxiolytic activity.

This and related arylpiperazine derivatives were described in patent literature as potentially useful in the treatment of CNS disorders such as anxiety and depression.

SOURCE – Universidad Complutense de Madrid, Madrid (ES).

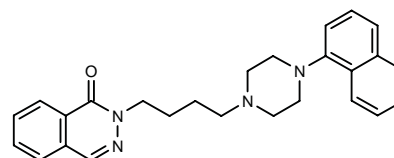
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- Lopez Rodriguez, M.L. et al. (Universidad Complutense de Madrid) *New arylpiperazine derivs*. ES 2095811, WO 9606846.
- Beneytez, M.E. et al. *Preliminary in vivo characterization of EF-7412, a pre- and postsynaptic 5HT_{1A} receptor antagonist*. Soc Neurosci Abst 1997, 23(Part 1): Abst 59.15.
- López-Rodríguez, M.L. et al. *Design and synthesis of a new antagonist at 5-HT_{1A} and D₂ receptors (EF-7412)*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.70.

ANTIPSYCHOTIC DRUGS

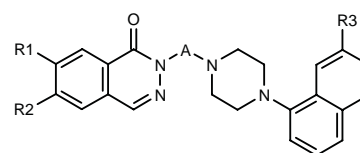
270174

2-[4-[4-(1-Naphthyl)piperazin-1-yl]butyl]-1(2*H*)-phthalazin-one



C26 H28 N4 O; Mol wt: 412.5342

ACTION – Antipsychotic agent with nanomolar affinity for 5-HT_{1A}, 5-HT₂ and dopamine D₂ receptors. Other specifically claimed compounds from this series of naphthylpiperazine derivatives include the following:



Compound	R1	R2	R3	A	Formula
270175	H	H	H	-(CH2)3-	C ₂₅ H ₂₆ N ₄ O
270176	H	H	H	-(CH2)2-	C ₂₄ H ₂₄ N ₄ O
270177	OMe	OMe	H	-(CH2)4-	C ₂₈ H ₃₂ N ₄ O ₃
270178	OMe	OMe	H	-(CH2)2-	C ₂₆ H ₂₈ N ₄ O ₃
270179	NO2	H	H	-(CH2)4-	C ₂₆ H ₂₇ N ₅ O ₃
270180	NH2	H	H	-(CH2)4-	C ₂₆ H ₂₉ N ₅ O
270181	NHAc	H	H	-(CH2)4-	C ₂₈ H ₃₁ N ₅ O ₂
270182	H	H	OMe	-(CH2)4-	C ₂₇ H ₃₀ N ₄ O ₂
270183	H	H	OMe	-(CH2)3-	C ₂₆ H ₂₈ N ₄ O ₂
270184	NO2	H	OMe	-(CH2)4-	C ₂₇ H ₂₉ N ₅ O ₄
270185	NO2	H	OMe	-(CH2)3-	C ₂₆ H ₂₇ N ₅ O ₄
270186	OMe	OMe	OMe	-(CH2)4-	C ₂₉ H ₃₄ N ₄ O ₄
270187	NO2	H	H	-(CH2)3-	C ₂₅ H ₂₆ N ₅ O ₃

SOURCE – FAES.

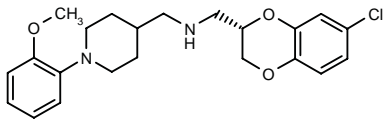
REFERENCES

1. Orjales Venero, A. and Garcia Dominguez, N. (FAES) *New naphthylpiperazine derivs. with antipsychotic activity*, EP 875512, JP 98287658.

BTS-79018

269638

N-[7-Chloro-1,4-benzodioxan-2(S)-ylmethyl]-N-[1-(2-methoxyphenyl)piperidin-4-ylmethyl]amine



C22 H27 Cl N2 O3; Mol wt: 402.9193

ACTION – Potential atypical antipsychotic agent that acts via preferential dopamine D₃ receptor antagonism and additional 5-HT_{1A} receptor partial agonism. In animal models predictive of antipsychotic efficacy, it inhibited apomorphine-induced climbing and amphetamine-induced hyperlocomotion with ED₅₀ values of 5.0 mg/kg p.o. and 1.8 mg/kg i.p., respectively, but it induced catalepsy only at much higher doses (ED₅₀ = 190 mg/kg i.p.), giving a therapeutic index 5-10-fold higher than that of olanzapine and risperidone.

SOURCE – Knoll.

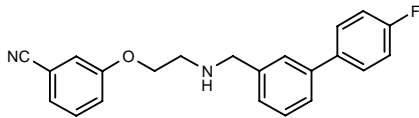
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1. Kerrigan, F. et al. (The Boots Company plc) *Bicyclic aromatic cpds. as therapeutic agents*. EP 717739, JP 97502431, US 5767116, WO 9507274.
2. Needham, P.L. et al. *BTS 79 018 - Advantaged pharmacological profile compared to new atypical antipsychotics*. Eur Neuropsychopharmacol 1998, 8(Suppl. 2): Abst P.2.026.

EMD-86006

269463

3-[2-[3-(4-Fluorophenyl)benzylamino]ethoxy]benzonitrile



C22 H19 F N2 O; Mol wt: 346.4031

ACTION – Dual 5-HT reuptake inhibitor and dopamine D₂ receptor antagonist, proven to inhibit 5-HT reuptake in mice with ID₅₀ values of 1.8 mg/kg s.c. and 2.4 mg/kg p.o. and to inhibit *p*-chloroamphetamine-induced hypothalamic 5-HT depletion in rats with ID₅₀ values of 0.4 mg/kg s.c. and 3.5 mg/kg p.o.; it bound to human dopamine D₂, D₃ and D₄ receptors with IC₅₀ values of 12, 3 and 3 nM, respectively, and stimulated the accumulation of DOPA in rat striatum (ED₅₀ = 3 mg/kg p.o.) but not in frontal cortex. Compound did not interact with dopamine D₁, 5-HT₁, 5-HT₂, 5-HT₃, σ-, histamine or excitatory amino acid receptors or α-adrenoceptors at concentrations of up to 300 nM. EMD-86006 inhibited marble-burying behavior in

mice (ED₅₀ = 1 mg/kg s.c., 4 mg/kg p.o.) and antagonized apomorphine-induced behaviors in rodents (ED₅₀ for climbing in mice = 1 mg/kg s.c., 5.4 mg/kg p.o.; ED₅₀ for stereotyped behavior in rats = 2.3 mg/kg s.c., 7.4 mg/kg p.o.). At effective doses it did not induce catalepsy. It is a candidate for the treatment of obsessive-compulsive and related disorders.

SOURCES – Lipha; Merck KGaA.

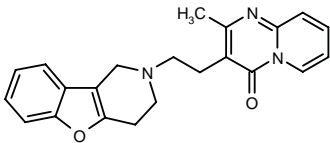
REFERENCES

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ANTIDEPRESSANTS

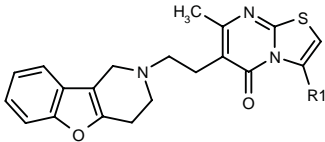
270036

2-Methyl-3-[2-(1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridin-2-yl)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one

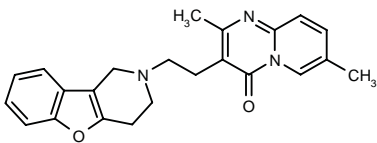


C22 H21 N3 O2; Mol wt: 359.4269

ACTION – Agent for the treatment or prevention of depression and Parkinson's disease, a potent antagonist of presynaptic α₂-adrenoceptors in the CNS. *In vivo*, it was found to reverse the loss of righting reflex induced by the α₂-adrenoceptor agonist xylazine in rats, with a lowest active dose (LAD = the lowest dose at which at least 66% of animals showed no loss of righting reflex) of 0.08 mg/kg s.c. and 0.31 mg/kg p.o. Within this series of 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine derivatives, the following are also specifically claimed:



Compound	R1	Formula
270037	H	C ₂₀ H ₁₉ N ₃ O ₂ S
270038	Me	C ₂₁ H ₂₁ N ₃ O ₂ S



270039: C23 H23 N3 O2

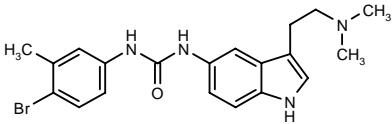
SOURCE – Janssen.

REFERENCES

1. Kennis, L.E.J. et al. (Janssen Pharmaceutica NV) *1,2,3,4-Tetrahydro-benzofuro[3,2-c]pyridine derivs*. WO 9845297.

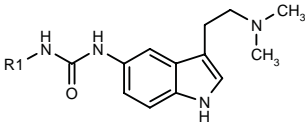
270634

N-(4-Bromo-3-methylphenyl)-*N'*-[3-[2-(dimethylamino)-ethyl]-1*H*-indol-5-yl]urea

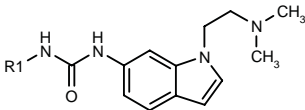


C20 H23 Br N4 O; Mol wt: 415.3327

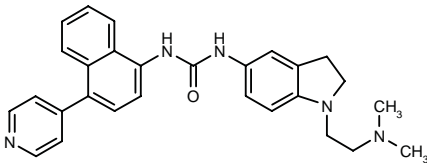
ACTION – Agent for the treatment or prevention of CNS disorders such as depression, anxiety, memory, eating and sleep disorders, and Parkinson’s disease, as well as endocrine disorders, vasospasm and hypertension, with combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor-antagonist activity (pK_i > 8.0 against the three receptors) and reported to possess a relatively fast onset of action. Within this series of heterocyclic urea derivatives, the following are also included:



Compound	R1	Formula
270635	2-Me-4-Pyr	C ₁₉ H ₂₃ N ₅ O
270636	2'-Me-4'-(5-Me-1,2,4-oxadiazol-3-yl)biphenyl-4-yl	C ₂₉ H ₃₀ N ₆ O ₂
270637	4-PhO-Ph	C ₂₅ H ₂₆ N ₄ O ₂
270638	4-(4-Pyr)-1-Naph	C ₂₈ H ₂₇ N ₅ O



Compound	R1	Formula
270639	2,3-(Cl)2-Ph	C ₁₉ H ₂₀ Cl ₂ N ₄ O
270640	4-(4-Pyr)-1-Naph	C ₂₈ H ₂₇ N ₅ O



270641: C28 H29 N5 O

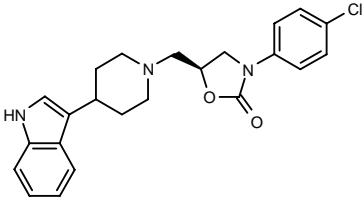
SOURCE – SmithKline Beecham.

REFERENCES

1. Gaster, L.M. and Wyman, P.A. (SmithKline Beecham plc) *Heterocycle-containing urea derivs. as 5HT_{1A}, 5HT_{1B} and 5HT_{1D} receptor antagonists*. WO 9847868.

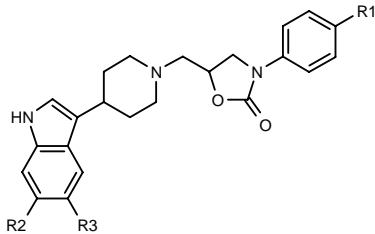
270901

(-)-3-(4-Chlorophenyl)-5(*S*)-[4-(1*H*-indol-3-yl)-1-piperidinylmethyl]oxazolidin-2-one



C23 H24 Cl N3 O2; Mol wt: 409.9146

ACTION – 5-HT_{2A} antagonist with additional 5-HT reuptake-inhibitory activity, potentially useful in the treatment of CNS disorders such as depression, anxiety, schizophrenia, panic attacks, obsessive–compulsive disorder, stroke and cerebral ischemia. Other specifically claimed compounds from this series of oxazolidine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
270902	CN	H	CN		C ₂₅ H ₂₃ N ₅ O ₂
270903	CN	F	H	S	C ₂₄ H ₂₃ FN ₄ O ₂
270905	CN	H	F	R	C ₂₄ H ₂₃ FN ₄ O ₂
270906	CN	F	H	R	C ₂₄ H ₂₃ FN ₄ O ₂
270907	H	H	CN		C ₂₄ H ₂₄ N ₄ O ₂
270908	H	F	H		C ₂₃ H ₂₄ FN ₃ O ₂

SOURCE – Merck KGaA.

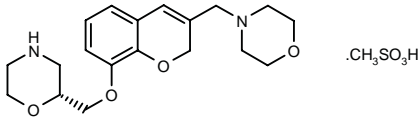
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1. Böttcher, H. et al. (Merck Patent GmbH) *Oxazolidines as 5-HT_{2A}-antagonists*. WO 9838189.

NAS-181

269373

(+)-2(*R*)-[3-(Morpholin-4-ylmethyl)-2*H*-1-benzopyran-8-yloxymethyl]morpholine methanesulfonate



C19 H26 N2 O4 . C H4 O3 S; Mol wt: 442.53

ACTION – Potent and selective, centrally acting 5-HT_{1B} receptor antagonist (K_i = 47 nM against [¹²⁵I]-iodocyanopindolol binding in rat cerebral cortex) with very low affinity for other 5-HT subtypes, α - and β -adrenoceptors and dopamine D₁ and D₂ receptors. In functional experiments in rat occipital cortex slices, compound potentiated K⁺-stimulated [³H]-5-HT release. In rat microdialysis studies, doses of 0.3-10 mg/kg s.c. enhanced the presynaptic release of 5-HT. Although it appears to be mainly useful as a pharmacological tool for evaluating the functional role of 5-HT_{1B} receptors, results from behavioral pharmacology studies indicated a potential antidepressant effect.

SOURCE – Astra Arcus.

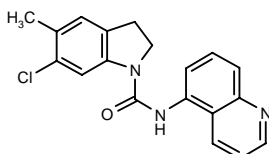
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2. Hillegaart, V. and Ahlenius, S. Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT_{1A} and 5-HT_{1B} receptor agonists 8-OH-DPAT and anpirtoline, as evidenced by use of the corresponding new and selective receptor antagonists NAS-299 and NAS-181. *Br J Pharmacol* 1998, 125(8): 1733.
3. Hjorth, S. In vivo rat brain microdialysis studies of the novel, selective 5-HT_{1B} receptor antagonist NAS-181. *Soc Neurosci Abst* 1998, 24(Part 1): Abst 438.13.
4. Wallsten, C.E. et al. Behavioral pharmacology of the new selective r5-HT_{1B} receptor antagonist NAS-181. *Soc Neurosci Abst* 1998, 24(Part 2): Abst 567.10.

SB-215505

269371

6-Chloro-5-methyl-N-(5-quinolinyl)-2,3-dihydro-1H-indole-1-carboxamide



C19 H16 Cl N3 O; Mol wt: 337.8084

ACTION – Potent and selective, surmountable 5-HT_{2B} receptor antagonist (pA_2 = 9.9 for inhibition of 5-HT_{2B}-mediated contractions of rat stomach fundus; pK_i = 7.9 for binding to rat 5-HT_{2C} receptors and 6.8 for binding to cloned human 5-HT_{2A} receptors). It antagonized two putative central 5-HT_{2B} receptor-mediated responses in rats at doses of 0.3 and 1 mg/kg p.o.: the BW-723C86-induced anxiolytic-like effect in a social interaction test and BW-723C86-induced hyperphagia in freely feeding animals; it was less effective in reversing mCPP-induced hypolocomotion in rats (central 5-HT_{2C}-mediated response), giving an ID₅₀ of 13 mg/kg p.o. Claimed in patent literature especially for the treatment of depression.

SOURCE – SmithKline Beecham.

REFERENCES

1. Ham, P. et al. (SmithKline Beecham plc) Indoline derivs. as 5HT_{2C} antagonists. EP 707581, JP 96512299, US 5834494, WO 9501976.
2. Kennett, G.A. (SmithKline Beecham plc) Novel treatment. WO 9831354.

3. Kennett, G.A. et al. SB-215505, a selective 5-HT_{2B} receptor antagonist in rats. *Soc Neurosci Abst* 1998, 24(Part 2): Abst 541.12.

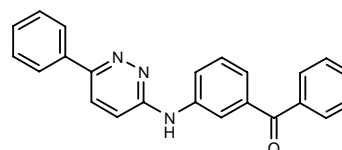
4. Reavill, C. et al. 5-HT_{2C} receptor antagonists, but not A 5-HT_{2A} or 5-HT_{2B} receptor antagonist, attenuate haloperidol-induced catalepsy in rat. *Br J Pharmacol* 1998, 125(Suppl.): Abst 65P.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

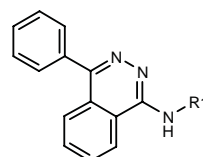
270066

3-(6-Phenylpyridazin-3-ylamino)benzophenone

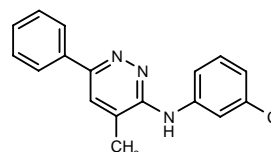


C23 H17 N3 O; Mol wt: 351.4073

ACTION – Anticonvulsant and anxiolytic agent with affinity for a novel receptor labeled by [³H]-SB-204269 in rat brain; it increased seizure threshold in the maximal electroshock seizure test in mice. Within this series of specifically claimed pyridazine and phthalazine derivatives, the following are also included.



Compound	R1	Formula
270068	2,6-(Cl)2-Ph	C ₂₀ H ₁₃ Cl ₂ N ₃
270069	2-t-Bu-Ph	C ₂₄ H ₂₃ N ₃
270070	3-CF ₃ O-Ph	C ₂₁ H ₁₄ F ₃ N ₃ O
270071	3-CN-Ph	C ₂₁ H ₁₄ N ₄
270072	3-Pyr	C ₁₉ H ₁₄ N ₄



270067: C17 H14 Cl N3

SOURCE – SmithKline Beecham.

REFERENCES

1. Harling, J.D. et al. (SmithKline Beecham plc) Pyridazine and phthalazine derivs., process of their preparation and their use as anticonvulsants. WO 9846574.

ACTION – Potent and selective, centrally acting 5-HT_{1B} receptor antagonist (K_i = 47 nM against [¹²⁵I]-iodocyanopindolol binding in rat cerebral cortex) with very low affinity for other 5-HT subtypes, α - and β -adrenoceptors and dopamine D₁ and D₂ receptors. In functional experiments in rat occipital cortex slices, compound potentiated K⁺-stimulated [³H]-5-HT release. In rat microdialysis studies, doses of 0.3-10 mg/kg s.c. enhanced the presynaptic release of 5-HT. Although it appears to be mainly useful as a pharmacological tool for evaluating the functional role of 5-HT_{1B} receptors, results from behavioral pharmacology studies indicated a potential antidepressant effect.

SOURCE – Astra Arcus.

REFERENCES

1. Berg, S. et al. (R)-(+)-2[[[3-(Morpholinomethyl)-2H-chromen-8-yl]oxy]methyl]morpholine methanesulfonate: A new selective rat 5-hydroxytryptamine1B receptor antagonist. J Med Chem 1998, 41(11): 1934.

2. Hillegaart, V. and Ahlenius, S. Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT_{1A} and 5-HT_{1B} receptor agonists 8-OH-DPAT and anpirtoline, as evidenced by use of the corresponding new and selective receptor antagonists NAS-299 and NAS-181. Br J Pharmacol 1998, 125(8): 1733.

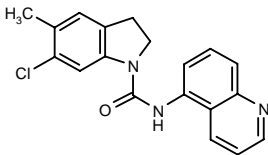
3. Hjorth, S. In vivo rat brain microdialysis studies of the novel, selective 5-HT_{1B} receptor antagonist NAS-181. Soc Neurosci Abst 1998, 24(Part 1): Abst 438.13.

4. Wallsten, C.E. et al. Behavioral pharmacology of the new selective r5-HT_{1B} receptor antagonist NAS-181. Soc Neurosci Abst 1998, 24(Part 2): Abst 567.10.

SB-215505

269371

6-Chloro-5-methyl-N-(5-quinolinyl)-2,3-dihydro-1H-indole-1-carboxamide



C19 H16 Cl N3 O; Mol wt: 337.8084

ACTION – Potent and selective, surmountable 5-HT_{2B} receptor antagonist (pA_2 = 9.9 for inhibition of 5-HT_{2B}-mediated contractions of rat stomach fundus; pK_i = 7.9 for binding to rat 5-HT_{2C} receptors and 6.8 for binding to cloned human 5-HT_{2A} receptors). It antagonized two putative central 5-HT_{2B} receptor-mediated responses in rats at doses of 0.3 and 1 mg/kg p.o.: the BW-723C86-induced anxiolytic-like effect in a social interaction test and BW-723C86-induced hyperphagia in freely feeding animals; it was less effective in reversing mCPP-induced hypolocomotion in rats (central 5-HT_{2C}-mediated response), giving an ID₅₀ of 13 mg/kg p.o. Claimed in patent literature especially for the treatment of depression.

SOURCE – SmithKline Beecham.

REFERENCES

1. Ham, P. et al. (SmithKline Beecham plc) Indoline derivs. as 5HT_{2C} antagonists. EP 707581, JP 96512299, US 5834494, WO 9501976.

2. Kennett, G.A. (SmithKline Beecham plc) Novel treatment. WO 9831354.

3. Kennett, G.A. et al. SB-215505, a selective 5-HT_{2B} receptor antagonist in rats. Soc Neurosci Abst 1998, 24(Part 2): Abst 541.12.

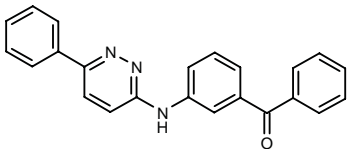
4. Reavill, C. et al. 5-HT_{2C} receptor antagonists, but not A 5-HT_{2A} or 5-HT_{2B} receptor antagonist, attenuate haloperidol-induced catalepsy in rat. Br J Pharmacol 1998, 125(Suppl.): Abst 65P.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

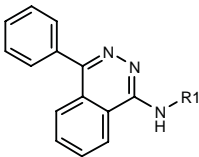
270066

3-(6-Phenylpyridazin-3-ylamino)benzophenone

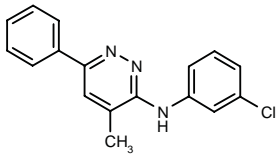


C23 H17 N3 O; Mol wt: 351.4073

ACTION – Anticonvulsant and anxiolytic agent with affinity for a novel receptor labeled by [³H]-SB-204269 in rat brain; it increased seizure threshold in the maximal electroshock seizure test in mice. Within this series of specifically claimed pyridazine and phthalazine derivatives, the following are also included.



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270069	2-t-Bu-Ph	C ₂₄ H ₂₃ N ₃
270070	3-CF3O-Ph	C ₂₁ H ₁₄ F ₃ N ₃ O
270071	3-CN-Ph	C ₂₁ H ₁₄ N ₄
270072	3-Pyr	C ₁₉ H ₁₄ N ₄



270067: C17 H14 Cl N3

SOURCE – SmithKline Beecham.

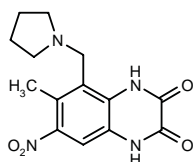
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PD-161989

269643

6-Methyl-7-nitro-5-(pyrrolidin-1-ylmethyl)-1,4-dihydro-quinoxaline-2,3-dione



C₁₄ H₁₆ N₄ O₄; Mol wt: 304.3044

ACTION – AMPA receptor antagonist, an analogue of PNQX with potent and long-lasting activity in inhibiting maximal electroshock-induced seizures in mice.

SOURCE – Warner-Lambert.

REFERENCES

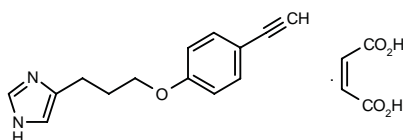
1. Kornberg, B.E. et al. (Warner-Lambert Co.) *Cyclic amine derivs. of subst. quinoxaline 2,3-diones as glutamate receptor antagonists*. WO 9640650.

2. Nikam, S.S. et al. *Design and synthesis of new AMPA/GLYN(N) receptor antagonists*. Soc Neurosci Abstr 1998, 24(Part 2): Abstr 504.13.

COGNITION-ENHANCING DRUGS

269367

4-[3-(4-Ethynylphenoxy)propyl]-1*H*-imidazole maleate



C₁₄ H₁₄ N₂ O . C₄ H₄ O₄; Mol wt: 342.3492

ACTION – Potent histamine H₃ receptor antagonist (K_i = 2.3 nM against K⁺-evoked [³H]-histamine release from rat cerebral cortex synaptosomes) with high selectivity over H₁ and H₂ receptors. It acted as a competitive H₃ receptor antagonist in a functional assay in guinea pig ileum (pA₂ = 8.1 ± 0.15). In an *in vivo* assay measuring the effect of compound on brain histamine turnover in mice, it was more active than thioperamide (ED₅₀ = 0.12 and 1.0 mg/kg p.o., respectively). Potentially useful for the therapy of H₃-dependent diseases of the CNS such as epilepsy, narcolepsy, schizophrenia and dementia.

SOURCES – Bioprojet; INSERM.

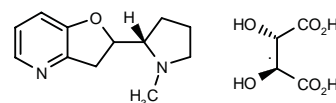
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2. Krause, M. et al. *4-Alkynylphenyl imidazolylpropyl ethers as selective histamine H₃-receptor antagonists with high oral central nervous system activity*. J Med Chem 1998, 41(21): 4171.

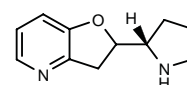
269771

2-[1-Methylpyrrolidin-2(*S*)-yl]-2,3-dihydrofuro[3,2-*b*]-pyridine D-(−)-tartrate

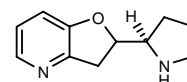


C₁₂ H₁₆ N₂ O . C₄ H₆ O₆; Mol wt: 354.3568

ACTION – Potent and selective nicotinic acetylcholine receptor ligand for the treatment of CNS and gastrointestinal disorders such as cognitive disorders, Parkinson's disease, tardive dyskinesias, schizophrenia, depression, anxiety, pain, Crohn's disease, ulcerative colitis and irritable bowel syndrome. Other compounds from this series of 2,3-dihydrofuro[3,2-*b*]pyridines are:



269772: C₁₁ H₁₄ N₂ O



270620: C₁₁ H₁₄ N₂ O

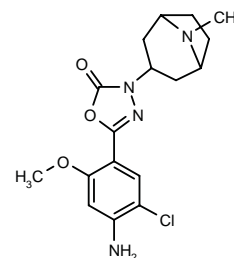
SOURCE – Synthélabo.

REFERENCES

1. Lochead, A. et al. (Synthélabo) *2,3-Dihydrofuro[3,2-*b*]pyridin, preparation and application thereof in therapy*. WO 9842713.

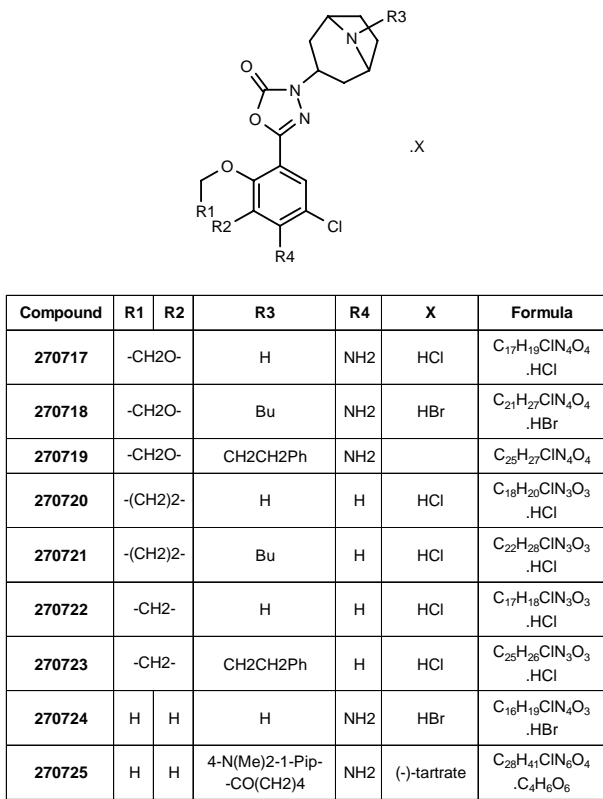
270716

5-(4-Amino-5-chloro-2-methoxyphenyl)-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,3,4-oxadiazol-2(3*H*)-one



C₁₇ H₂₁ Cl N₄ O₃; Mol wt: 364.8309

ACTION – Agent for the treatment of CNS disorders including cognitive disorders, psychoses, obsessive-compulsive disorder, depression and anxiety, as well as gastrointestinal disorders such as irritable bowel syndrome, urinary tract disorders such as urinary incontinence and cardiovascular disorders such as arrhythmia and hypertension, that possesses affinity for 5-HT₄ and/or histamine H₃ receptors. Other compounds from this series of 5-aryl-3-(8-azabicyclo[3.2.1]oct-3-yl)-1,3,4-oxadiazol-2(3*H*)-one derivatives include the following:



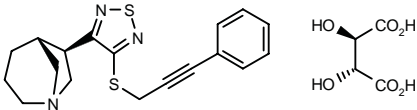
SOURCE – Synthélabo.

REFERENCES

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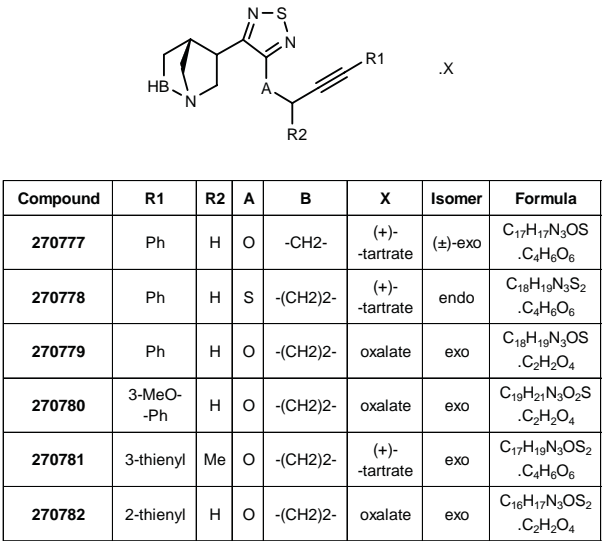
270776

exo-(5*R*,6*R*)-6-[4-(3-Phenyl-2-propynylsulfanyl)-1,2,5-thiadiazol-3-yl]-1-azabicyclo[3.2.1]octane L-(+)-tartrate



C18 H19 N3 S2 . C4 H6 O6; Mol wt: 491.5865

ACTION – Cognition-enhancing agent, a potent and selective muscarinic M₁ receptor agonist, as demonstrated by its ability to stimulate phosphoinositol hydrolysis in A9L cells transfected with the human M₁ receptor (EC₅₀ = 0.2 nM; efficacy = 105% [carbachol 100 μM = 99%]). Also potentially useful for the treatment of severe painful conditions, glaucoma, psychosis, schizophrenia, anxiety, sleep disorders and bladder dysfunction. Within this series of heterocyclic compounds, the following are also included:



SOURCE – Novo Nordisk.

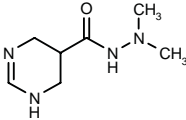
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CDD-0125-A

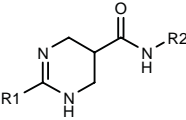
270329

N',N'-Dimethyl-1,4,5,6-tetrahydro-5-pyrimidinecarbohydrazide



C7 H14 N4 O; Mol wt: 170.2146

ACTION – CNS muscarinic receptor agonist (IC₅₀ = 3.7 μM against [³H]-QNB binding in rat brain preparations). Other exemplified amidine derivatives include the following:



Compound	R1	R2	Formula
CDD-0131-A [270330]	H	Me	C ₈ H ₁₁ N ₃ O
CDD-0126-A [270331]	NH2	N(Me)2	C ₇ H ₁₅ N ₅ O

SOURCE – University of Toledo, Toledo, OH (US).

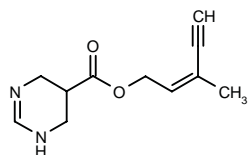
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CDD-0162-A

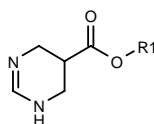
270332

1,4,5,6-Tetrahydro-5-pyrimidinecarboxylic acid (Z)-3-methyl-2-penten-4-ynyl ester



C11 H14 N2 O2; Mol wt: 206.2436

ACTION – CNS muscarinic receptor agonist ($IC_{50} = 1.5 \pm 0.42 \mu M$ against $[^3H]$ -QNB binding in rat brain preparations) from a series of amidine derivatives, wherein the following are also included:



Compound	R1	Formula
CDD-0161-A [270333]	(E)-CH ₂ CH=C(ethynyl)Me	C ₁₁ H ₁₄ N ₂ O ₂
CDD-0171-A [270334]	2-butyryl	C ₉ H ₁₂ N ₂ O ₂

SOURCE – University of Toledo, Toledo, OH (US).

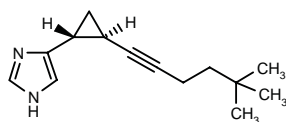
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- Messer, W.S. Jr. and Ojo, B. (University of Toledo) *Muscarinic agonists*. WO 9846232.

GT-2331

262321

(R,R)-4-[2-(5,5-Dimethyl-1-hexynyl)cyclopropyl]-1H-imidazole



C14 H20 N2; Mol wt: 216.326

ACTION – Agent for the treatment of CNS disorders involving disturbances in arousal and cognitive function, a potent histamine H₃ receptor antagonist ($K_i = 0.12 \pm 0.04$ nM) with excellent selectivity relative to H₁ and H₂ receptors. Compound showed good CNS penetration with oral ED₅₀s of 0.12 and 0.22 mg/kg, respectively, for H₃ receptor occupancy in mouse and rat cortex. In a functional assay (H₃ receptor-mediated inhibition of neurogenic contractions of guinea pig ileum), compound showed high antagonist potency ($pA_2 = 8.5$). Compound is being evaluated in phase I human clinical trials and its development is targeted at disorders such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and sleep disorders.

SOURCE – Gliatech.

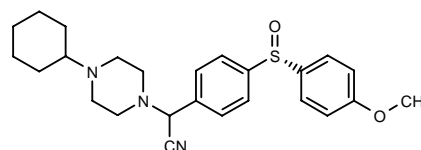
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- Gliatech's first drug candidate begins phase I clinical trials*. Prous Science Daily Essentials 1998, Nov 6.

SCH-57790

269372

2-(4-Cyclohexylpiperazin-1-yl)-2-[4-[(S)-4-methoxyphenylsulfenyl]phenyl]acetonitrile



C25 H31 N3 O2 S; Mol wt: 437.6049

ACTION – Potent muscarinic M₂ receptor antagonist, as demonstrated in binding studies using cloned human M₂ receptors expressed in CHO cells by K_i values of 3-10 nM, with 40-50-fold selectivity over M₁ receptors; binding to M₂ receptors was competitive and stereoselective. *In vivo* in microdialysis studies, compound dose-dependently (0.1-10 mg/kg i.p. or p.o.) increased acetylcholine release from both rat cortex and striatum. In behavioral studies such as the rat passive avoidance task (0.003-1.0 mg/kg) and the rat water maze (0.003-0.3 mg/kg/day for 5 days), it improved cognitive performance, and it also improved working memory in an operant task in squirrel monkeys at doses of 0.01-0.03 mg/kg/day for 4 days. Sch-57790 was devoid of mydriasis (M₁ receptor-mediated effect) at doses of up to 10 mg/kg. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Schering-Plough.

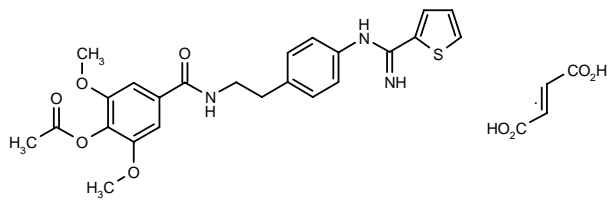
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TREATMENT OF
CEREBROVASCULAR DISEASES

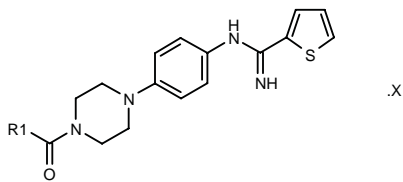
269604

4-Acetoxy-*N*-[2-[4-[imino(2-thienyl)methylamino]-phenyl]ethyl]-3,5-dimethoxybenzamide fumarate

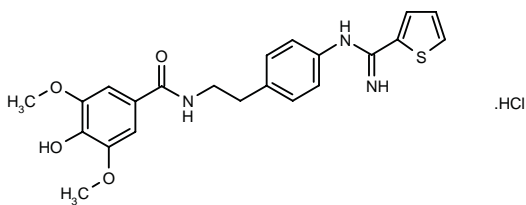


C24 H25 N3 O5 S . C4 H4 O4; Mol wt: 583.6151

ACTION – Agent for the treatment of cerebrovascular and cardiovascular disorders, a lipid peroxidation inhibitor and inhibitor of nitric oxide synthase (NOS) such as neuronal constitutive NOS (ncNOS) from rat cerebellum (IC₅₀ < 3.5 μM). Within this series of specifically claimed 2-(iminomethyl)amino-phenyl derivatives, the following are also included:



Compound	R1	X	Formula
269606	2,5,7,8-(Me)4-6-OH- -3,4-dihydro-2H-benzopyran-2-yl	HCl	C ₂₉ H ₃₄ N ₄ O ₃ S.HCl
269607	5-MeO-3-indolyl-CH2		C ₂₆ H ₂₇ N ₅ O ₂ S



269605: C22 H23 N3 O4 S . HCl

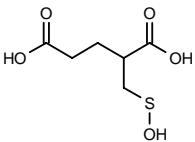
SOURCE – SCRAS.

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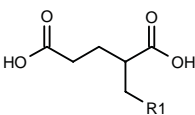
269909

2-(Sulfenomethyl)pentadienoic acid



C6 H10 O5 S; Mol wt: 194.206

ACTION – Agent for the treatment of prostate diseases, particularly prostate cancer, and glutamate abnormalities such as epilepsy, stroke, Alzheimer's disease, Parkinson's disease and ischemia that acts by inhibiting *N*-acetylated α-linked acidic dipeptidase (NAALADase) activity. Within this series of specifically claimed thio derivatives, the following are also included:



Compound	R1	Formula
269910	SOMe	C ₇ H ₁₂ O ₅ S
269911	SOPh	C ₁₂ H ₁₄ O ₅ S
269912	SO(CH2)3Ph	C ₁₅ H ₂₀ O ₅ S
269913	4-Pyr-SO	C ₁₁ H ₁₃ NO ₅ S
270704	SO2H	C ₆ H ₁₀ O ₆ S
270705	SO2Et	C ₈ H ₁₄ O ₆ S
270706	SO2Bu	C ₁₀ H ₁₈ O ₆ S
270707	SO2CH2CH2Ph	C ₁₄ H ₁₈ O ₆ S
270708	SO(=NH)Pr	C ₉ H ₁₇ NO ₅ S
270709	SO(=NH)CH2CH2Ph	C ₁₄ H ₁₉ NO ₅ S
270710	SO(=NH)CH2Ph	C ₁₃ H ₁₇ NO ₅ S

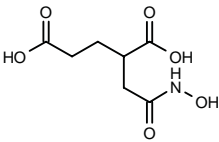
SOURCE – Guilford.

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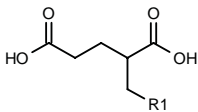
269924

2-(*N*-Hydroxycarbamoylmethyl)pentanedioic acid



C7 H11 N O6; Mol wt: 205.1649

ACTION – Agent for the treatment of prostate diseases, particularly prostate cancer, and glutamate abnormalities such as epilepsy, stroke, Parkinson's disease, Alzheimer's disease and ischemia that acts by inhibiting *N*-acetylated α-linked acidic dipeptidase (NAALADase) activity. Within this series of hydroxamic acid derivatives, the following are also included:



Compound	R1	Formula
269925	CON(OH)Bu	C ₁₁ H ₁₉ NO ₆
269926	CON(OH)CH ₂ CH ₂ Ph	C ₁₅ H ₁₉ NO ₆
269927	4-Pyr-N(OH)CO	C ₁₂ H ₁₄ N ₂ O ₆
269928	N(OH)CHO	C ₇ H ₁₁ NO ₆
269929	N(OH)COCH ₂ Ph	C ₁₄ H ₁₇ NO ₆
269930	N(OH)COPr	C ₁₀ H ₁₇ NO ₆
269931	N(OH)CO(CH ₂) ₃ Ph	C ₁₆ H ₂₁ NO ₆

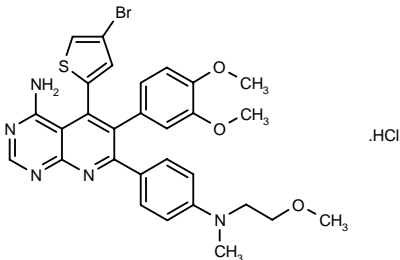
SOURCE – Guilford.

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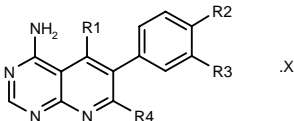
270388

5-(4-Bromo-2-thienyl)-6-(3,4-dimethoxyphenyl)-7-[4-[N-(2-methoxyethyl)-N-methylamino]phenyl]pyrido[2,3-*d*]-pyrimidin-4-amine hydrochloride



C29 H28 Br N5 O3 S . HCl; Mol wt: 643.0031

ACTION – Adenosine kinase inhibitor (IC₅₀ = 0.1 nM) potentially useful for the treatment of cerebral and myocardial ischemia, angina, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility, as well as for use in coronary artery bypass graft (CABG) surgery and percutaneous transluminal angioplasty (PTCA). Other compounds from this series of 5,6,7-trisubstituted-4-aminopyrido[2,3-*d*]pyrimidines include the following:



Compound	R1	R2=R3	R4	X	Formula
270389	3-Br-Ph	OMe	2-thienyl		C ₂₅ H ₁₉ BrN ₄ O ₂ S
270390	4-Br-2-thienyl	OMe	2-thienyl		C ₂₃ H ₁₇ BrN ₄ O ₂ S ₂
270391	3-Cl-Ph	OMe	2-thienyl	HCl	C ₂₅ H ₁₉ ClN ₄ O ₂ S .HCl
270392	3-Br-Ph	H	6-(4-morpholinyl)-3-Pyr	HCl	C ₂₈ H ₂₃ BrN ₆ O .HCl

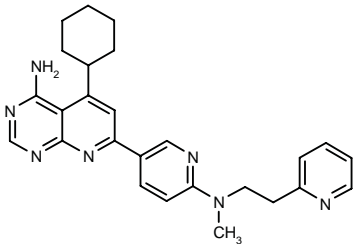
SOURCE – Abbott.

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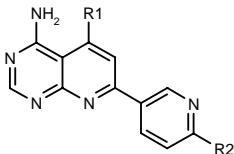
270393

5-Cyclohexyl-7-[6-[N-methyl-N-[2-(2-pyridyl)ethyl]-amino]pyridin-3-yl]pyrido[2,3-*d*]pyrimidin-4-amine



C26 H29 N7; Mol wt: 439.5641

ACTION – Adenosine kinase inhibitor (IC₅₀ = 0.1 nM) potentially useful for the treatment of cerebral and myocardial ischemia, angina, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility, as well as for use in coronary artery bypass graft (CABG) surgery and percutaneous transluminal angioplasty (PTCA). Within this series of 5,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidine derivatives, the following are also included:



Compound	R1	R2	Formula
270394	2-Br-PhCH(Me)	4-morpholinyl	C ₂₄ H ₂₃ BrN ₆ O
270395	2-Br-PhCH ₂	4-morpholinyl	C ₂₃ H ₂₁ BrN ₆ O
270396	cyclohexyl	4-Ac-1-Piz	C ₂₄ H ₂₉ N ₇ O
270397	cyclohexyl	2-(MeOCH ₂)-1-pyrrolidinyl	C ₂₄ H ₃₀ N ₆ O

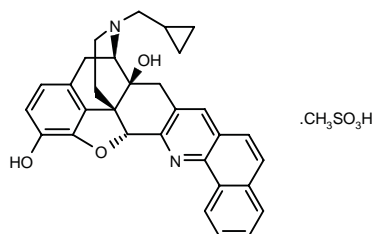
SOURCE – Abbott.

REFERENCES

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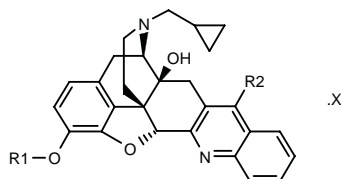
270443

17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14 β -dihydroxy-6,7-didehydrobenzo[7',8']quino[2',3':6,7]morphinan methane-sulfonate



C31 H28 N2 O3 . C H4 O3 S; Mol wt: 572.6788

ACTION – Agent for the treatment or prevention of cerebrovascular disorders such as stroke, brain edema, traumatic brain injury and neurodegenerative disorders whose activity was demonstrated *in vivo* by inhibition of cerebral infarction following middle cerebral artery occlusion and reperfusion in rats (62% inhibition at 0.3 mg/kg i.p. administered prior to occlusion; 89% inhibition at 3 mg/kg i.p. administered after reperfusion). A representative compound from a series of quinolinomorphinan derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
270444	H	NH2	HCl	C ₂₇ H ₂₇ N ₃ O ₃ .HCl
270445	Me	NH2	HCl	C ₂₈ H ₂₉ N ₃ O ₃ .HCl
270446	H	Me	MeSO3H	C ₂₈ H ₂₈ N ₂ O ₃ .CH ₃ O ₃ S

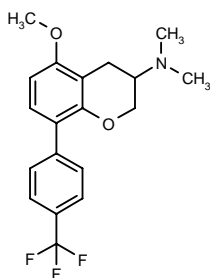
SOURCE – Toray.

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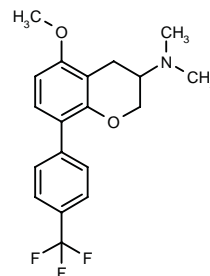
270727

(-)-N-[5-Methoxy-8-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2H-1-benzopyran-3-yl]-N,N-dimethylamine



C19 H20 F3 N O2; Mol wt: 351.366

ACTION – Agent for the treatment of epilepsy, stroke and brain or spinal trauma, reported to bind to veratridine-sensitive sodium channels and to block veratridine-induced glutamate release in rat hippocampal slice preparations at concentrations of 0.1-1 μ M. The compound provided long-lasting protection against maximal electroshock-induced convulsions in mice with a threshold dose of 10 mg/kg p.o. and 100% protection at 32 mg/kg p.o. In the middle cerebral artery (MCA) occlusion model in rats, it was found to reduce infarct size by 25% when given 5 min after occlusion at about 4.5 mg/kg i.v. Other compounds within this series of chroman derivatives include the following:



Compound	Isomer	Formula
270728	racemic	C ₁₉ H ₂₀ F ₃ NO ₂
270729	(+)	C ₁₉ H ₂₀ F ₃ NO ₂

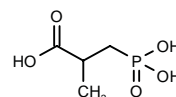
SOURCE – Novartis.

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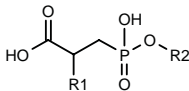
270730

2-Methyl-3-phosphonopropionic acid



C4 H9 O5 P; Mol wt: 168.0841

ACTION – Agent for the treatment of glutamate abnormalities including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, schizophrenia, pain and, particularly, ischemia, as well as prostate disorders such as prostatic cancer or benign prostatic hyperplasia, that acts by inhibiting *N*-acetylated α -linked acidic dipeptidase (NAALADase) enzyme activity. Other specifically claimed compounds from this series of phosphonic acid derivatives include the following:



Compound	R1	R2	Formula
270731	Et	H	C ₅ H ₁₁ O ₅ P
270732	Pr	H	C ₆ H ₁₃ O ₅ P
270733	Bu	H	C ₇ H ₁₅ O ₅ P
270734	Ph	H	C ₉ H ₁₁ O ₅ P
270735	CH ₂ CH ₂ Ph	H	C ₁₁ H ₁₅ O ₅ P
270736	(CH ₂) ₃ Ph	H	C ₁₂ H ₁₇ O ₅ P
270737	4-Pyr	H	C ₈ H ₁₀ NO ₅ P
270738	CH ₂ Ph	H	C ₁₀ H ₁₃ O ₅ P
270739	CH ₂ CH ₂ CO ₂ H	Me	C ₇ H ₁₃ O ₇ P
270740	CH ₂ CH ₂ CO ₂ H	Et	C ₈ H ₁₅ O ₇ P
270741	CH ₂ CH ₂ CO ₂ H	Pr	C ₉ H ₁₇ O ₇ P
270742	CH ₂ CH ₂ CO ₂ H	Bu	C ₁₀ H ₁₉ O ₇ P
270743	CH ₂ CH ₂ CO ₂ H	Ph	C ₁₂ H ₁₅ O ₇ P
270744	CH ₂ CH ₂ CO ₂ H	CH ₂ CH ₂ Ph	C ₁₄ H ₁₉ O ₇ P
270745	CH ₂ CH ₂ CO ₂ H	(CH ₂) ₃ Ph	C ₁₅ H ₂₁ O ₇ P
270746	CH ₂ CH ₂ CO ₂ H	4-Pyr	C ₁₁ H ₁₄ NO ₇ P
270747	CH ₂ CH ₂ CO ₂ H	CH ₂ Ph	C ₁₃ H ₁₇ O ₇ P

SOURCE – Guilford.

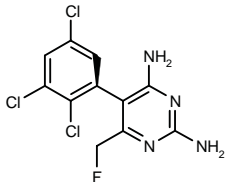
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BW-202W92

267798

(–)-6-(Fluoromethyl)-5-(2,3,5-trichlorophenyl)pyrimidine-2,4-diamine



C11 H8 Cl3 F N4; Mol wt: 321.5692

ACTION – Sodium channel inhibitor with neuroprotective activity in a rat model of focal cerebral ischemia induced by permanent middle cerebral artery occlusion. A potential follow-up compound to BW-619C89.

SOURCE – Glaxo Wellcome.

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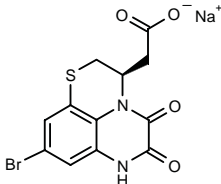
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CGP-68730A

269457

236420⁺ (as undefined isomer)

2-[9-Bromo-5,6-dioxo-2,3,6,7-tetrahydro-5*H*-[1,4]thiazino-[4,3,2-*de*]quinoxalin-3(*R*)-yl]acetic acid sodium salt



C12 H8 Br N2 Na O4 S ; Mol wt: 379.1652

ACTION – Glycine-site NMDA receptor antagonist proven to bind to human NMDA NR1A/2A and NR1A/2B subtypes with IC₅₀ values below 1 μM, without subtype selectivity. Compound antagonized NMDA-induced depolarizations in neocortical slices and epileptiform activity in hippocampal slices *in vitro*, as well as NMDA-induced excitation in the CA1 region following iontophoretic application, whereas only weak effects were observed in the latter test following i.v. application, indicating poor central activity.

SOURCE – Novartis.

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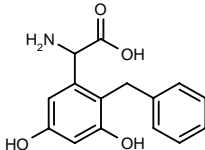
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*Drug Data Report 1996, 018(07): 0601.

LY-339476

267807

2-Amino-2-(2-benzyl-3,5-dihydroxyphenyl)acetic acid



C15 H15 N O4; Mol wt: 273.2865

ACTION – A 3,5-dihydroxyphenylglycine (3,5-DHPG) derivative with moderate antagonist activity at the metabotropic glutamate mGluR1α receptor subtype, as demonstrated by inhibition of quisqualate-induced phosphoinositide hydrolysis in cell lines expressing this receptor (IC₅₀ = 124 μM), and selectivity relative to the mGluR5a subtype (IC₅₀ > 1000 μM). Potentially useful for the treatment of neurodegenerative disorders such as stroke, cerebral ischemia, head and spinal cord trauma, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, AIDS-related dementia and Huntington’s chorea, and as an antipsychotic, anticonvulsant, antiemetic, analgesic, anxiolytic and antidepressant agent.

SOURCE – Lilly.

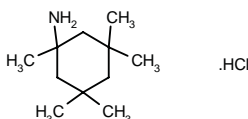
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MRZ-2/579

270075

1,3,3,5,5-Pentamethylcyclohexylamine hydrochloride



C11 H23 N . HCl; Mol wt: 205.7706

ACTION – Uncompetitive NMDA receptor antagonist (IC_{50} = 1.3 μ M) with no subtype selectivity. Compound protected against glutamate-induced neurotoxicity in cultured rat cortical neurons. It has a similar profile to memantine in preclinical models of disturbed glutamatergic transmission. In rats, it showed strong neuroprotective activity, therapeutic potential in opioid abuse and antiparkinsonian-like activity.

SOURCE – Merz.

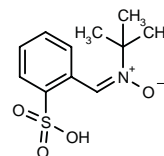
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2. Hölter, S.M. et al. *The uncompetitive NMDA-receptor antagonist MRZ 2/579 suppresses the alcohol deprivation effect in rats*. Alcohol Clin Exp Res 1998, 22(3, Suppl.): Abst 536.
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SPBN

269374

N-(*tert*-Butyl)- α -(2-sulphophenyl)nitrone



C11 H15 N O4 S; Mol wt: 257.3085

ACTION – Free radical scavenger able to protect against secondary apoptotic damage in a model of head injury in immature rat brain. When given at doses of 30-100 mg/kg 1 and 13 h after trauma, it protected against apoptotic damage, exhibiting an effect similar to *N*-acetylcysteine (400-600 mg/kg) or pentoxifylline (50-100 mg/kg). Potentially useful in the treatment of pediatric head trauma.

SOURCES – Eisai; Humboldt Universität, Berlin (DE); University College London, London (GB).

REFERENCES

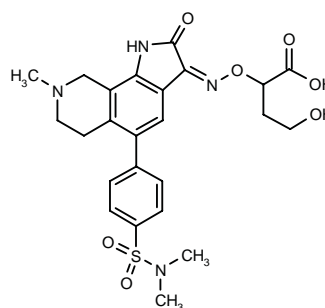
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SPD-502

264182

5-[4-(Dimethylaminosulfonyl)phenyl]-8-methyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline-2,3-dione 3-*O*-(4-hydroxy-2-butanoyl)oxime

NS-1209



C24 H28 N4 O7 S; Mol wt: 516.5722

ACTION – Competitive AMPA receptor antagonist with an IC_{50} of 43 nM for inhibition of [3 H]-AMPA binding, low affinity for the [3 H]-kainate binding site (IC_{50} = 54 μ M) and no affinity for both NMDA and glycine binding sites. Compound inhibited AMPA-induced [3 H]-GABA release from cortical neurons (IC_{50} = 0.22 μ M), AMPA-induced depolarization in rat cortical wedge preparations (IC_{50} = 0.16 μ M) and AMPA-evoked spike responses in mouse cortical neurons (IC_{50} = 0.14 μ M). *In vivo* in rat hippocampus, compound induced potent and long-lasting inhibition of AMPA-evoked single neuron spike activity. In models of focal cerebral ischemia in rats and global cerebral ischemia in gerbils, compound administered by i.v. bolus followed by constant i.v. infusion starting up to 2 h after occlusion provided significant protection of hippocampal CA1 neurons. It is undergoing preclinical evaluation for the acute treatment of stroke.

SOURCES – NeuroSearch; Shire Laboratories.

REFERENCES

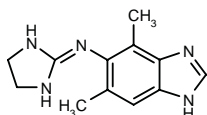
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9. *Shire: six-month highlights.* Prous Science Daily Essentials 1998, Sept 10.
10. NeuroSearch A/S Annual Report 1997

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

270398

5-(Imidazolidin-2-ylideneamino)-4,6-dimethyl-1H-benzimidazole



C₁₂ H₁₅ N₅; Mol wt: 229.2855

ACTION – A specifically claimed compound within a series of 5-(2-imidazolinylamino)benzimidazole derivatives with α_2 -adrenoceptor-agonist activity, expected to be particularly useful in the treatment of nasal congestion.

SOURCE – Procter & Gamble.

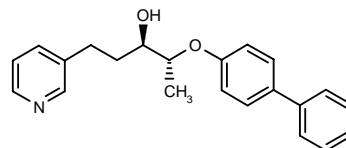
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ASTHMA THERAPY

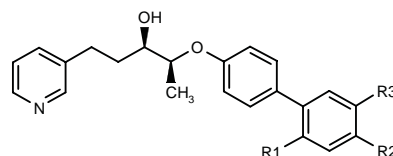
269676

(3*R*,4*R*)-4-(Biphenyl-4-yloxy)-1-(3-pyridyl)-3-pentanol

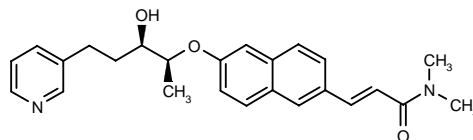


C₂₂ H₂₃ N O₂; Mol wt: 333.4287

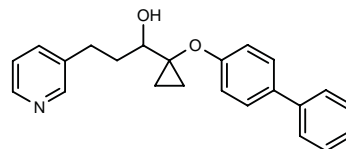
ACTION – Agent for the prevention or treatment of allergic, inflammatory, autoimmune, proliferative and hyperproliferative diseases that acts by inhibiting the activation of hematopoietic cells such as mast cells, neutrophils and eosinophils; it is reported to inhibit histamine release from mast cells with an IC₅₀ < 10 μ M. Within this series of specifically claimed pyridine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269677	H	H	CN	C ₂₃ H ₂₂ N ₂ O ₂
269678	H	F	H	C ₂₂ H ₂₂ FNO ₂
269680	Me	H	OMe	C ₂₄ H ₂₇ NO ₃
269681	H	H	SO ₂ NHCH ₂ -CH ₂ N(Me) ₂	C ₂₈ H ₃₃ N ₃ O ₄ S
269682	H	H	4-morpholinyl-COCH ₂	C ₂₈ H ₃₂ N ₂ O ₄
269683	H	CN	Me	C ₂₄ H ₂₄ N ₂ O ₂
269685	H	NHCONH ₂	H	C ₂₃ H ₂₅ N ₃ O ₃
269686	H	H	N(Me)COCF ₃	C ₂₅ H ₂₅ F ₃ N ₂ O ₃



269684: C₂₅ H₂₈ N₂ O₃



269679: C₂₃ H₂₃ N O₂

SOURCE – Astra.

REFERENCES

1. Cheshire, D. et al. (Astra AB) *Novel pyridine derivs. and pharmaceutical compsns. containing them.* WO 9842670.

SOURCES – NeuroSearch; Shire Laboratories.

REFERENCES

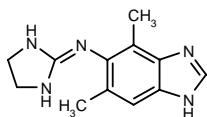
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2. Drejer, J. *Therapeutic opportunities in AMPA/KAIN antagonists.* New Dev Glutamate Pharmacol (April 23-24, San Francisco) 1998.
3. Johansen, T.H. et al. *Pharmacological characterization of SPD 502: A novel competitive AMPA receptor antagonist.* Soc Neurosci Abst 1998, 24(Part 1): Abst 229.13.
4. Jones, B.E. et al. *Neuroprotective profile of SPD-502: A potent and water soluble selective AMPA antagonist.* Soc Neurosci Abst 1998, 24(Part 1): Abst 382.13.
5. Olsen, G.M. et al. *SPD502, a new selective AMPA antagonist, reduces infarct size and protects against CA1 cell loss in rodents following focal and global ischemia.* Soc Neurosci Abst 1998, 24(Part 1): Abst 230.6.
6. *NeuroSearch signs agreement with Shire for CNS compounds.* Prous Science Daily Essentials 1998, Feb 9.
7. *NeuroSearch: year-end 1997 highlights.* Prous Science Daily Essentials 1998, March 17.
8. *Shire: Interim Report 1997.* Prous Science Daily Essentials 1998, March 20.
9. *Shire: six-month highlights.* Prous Science Daily Essentials 1998, Sept 10.
10. NeuroSearch A/S Annual Report 1997

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

270398

5-(Imidazolidin-2-ylideneamino)-4,6-dimethyl-1H-benzimidazole



C₁₂ H₁₅ N₅; Mol wt: 229.2855

ACTION – A specifically claimed compound within a series of 5-(2-imidazolinylamino)benzimidazole derivatives with α_2 -adrenoceptor-agonist activity, expected to be particularly useful in the treatment of nasal congestion.

SOURCE – Procter & Gamble.

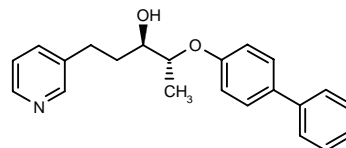
REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) *5-(2-Imidazolinylamino)benzimidazole cpds. useful as α_2 -adrenoceptor agonists.* WO 9846595.

ASTHMA THERAPY

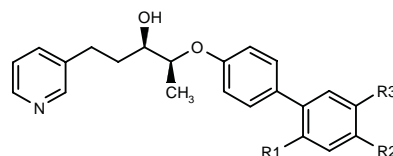
269676

(3*R*,4*R*)-4-(Biphenyl-4-yloxy)-1-(3-pyridyl)-3-pentanol

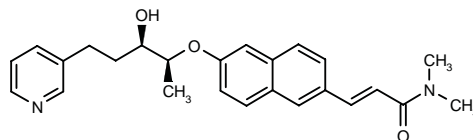


C₂₂ H₂₃ N O₂; Mol wt: 333.4287

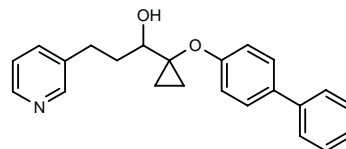
ACTION – Agent for the prevention or treatment of allergic, inflammatory, autoimmune, proliferative and hyperproliferative diseases that acts by inhibiting the activation of hematopoietic cells such as mast cells, neutrophils and eosinophils; it is reported to inhibit histamine release from mast cells with an IC₅₀ < 10 μ M. Within this series of specifically claimed pyridine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269677	H	H	CN	C ₂₃ H ₂₂ N ₂ O ₂
269678	H	F	H	C ₂₂ H ₂₂ FNO ₂
269680	Me	H	OMe	C ₂₄ H ₂₇ NO ₃
269681	H	H	SO ₂ NHCH ₂ -CH ₂ N(Me) ₂	C ₂₈ H ₃₃ N ₃ O ₄ S
269682	H	H	4-morpholinyl-COCH ₂	C ₂₈ H ₃₂ N ₂ O ₄
269683	H	CN	Me	C ₂₄ H ₂₄ N ₂ O ₂
269685	H	NHCONH ₂	H	C ₂₃ H ₂₅ N ₃ O ₃
269686	H	H	N(Me)COCF ₃	C ₂₅ H ₂₅ F ₃ N ₂ O ₃



269684: C₂₅ H₂₈ N₂ O₃



269679: C₂₃ H₂₃ N O₂

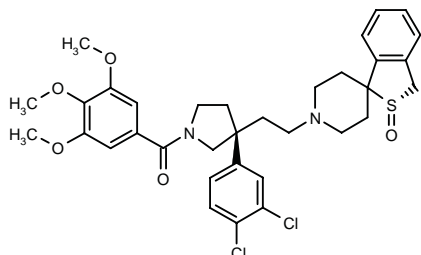
SOURCE – Astra.

REFERENCES

1. Cheshire, D. et al. (Astra AB) *Novel pyridine derivs. and pharmaceutical compsns. containing them.* WO 9842670.

269857

1'-[2-[3-(S)-(3,4-Dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidin-3-yl]ethyl]spiro[benzo[c]thiophene-1(3H)-4'-piperidine] 2(S)-oxide



C34 H38 Cl2 N2 O5 S; Mol wt: 657.6552

ACTION – Agent for the treatment of asthma, bronchitis, rhinitis, allergy and urinary incontinence, an NK₁ and NK₂ receptor antagonist with respective IC₅₀ values of 5.5 and 5.8 ng/ml in binding assays.

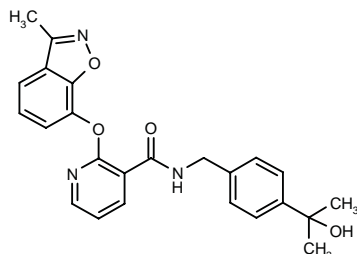
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Pyrrolidine derivs.* JP 98273489.

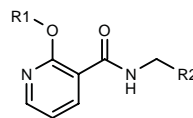
269971

N-[4-(1-Hydroxy-1-methylethyl)benzyl]-2-(3-methyl-1,2-benzisoxazol-7-yloxy)pyridine-3-carboxamide



C24 H23 N3 O4; Mol wt: 417.4627

ACTION – A selective inhibitor of phosphodiesterase type 4 (PDE4), particularly the PDE4D isozyme involved in regulating the activation and degranulation of human eosinophils, and of tumor necrosis factor (TNF). Potentially useful for the treatment of asthma, as well as a wide range of other inflammatory, allergic, respiratory and other disorders. Other specifically claimed compounds from this series of nicotinamide derivatives include the following:



Compound	R1	R2	Formula
269972	3-[MeON=C(Me)]-Ph	4-[C(Me)2OH]-Ph	C ₂₅ H ₂₇ N ₃ O ₄
269973	4-F-Ph	2-Cl-Ph	C ₁₉ H ₁₄ ClFN ₂ O ₂
269974	4-F-Ph	4-[C(Me)2OH]-Ph	C ₂₂ H ₂₁ FN ₂ O ₃
269975	3-Ac-Ph	4-[C(Me)2OH]-cyclohexyl	C ₂₄ H ₃₀ N ₂ O ₄
269976	1,3-benzodioxol-5-yl	4-[CH(OH)Me]-cyclohexyl	C ₂₂ H ₂₆ N ₂ O ₅
269977	1,3-benzodioxol-5-yl	4-[C(Me)2OH]-Ph	C ₂₃ H ₂₂ N ₂ O ₅
269978	3-Pyr	4-[C(Me)2OH]-Ph	C ₂₁ H ₂₁ N ₃ O ₃

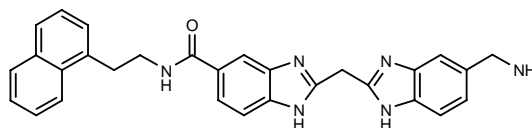
SOURCE – Pfizer.

REFERENCES

1. Chambers, R.J. et al. (Pfizer Inc.) *Nicotinamide derivs.* WO 9845268.

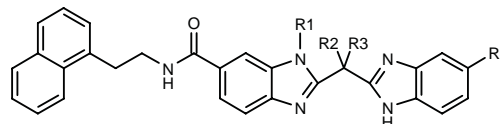
269988

2-[5-(Aminomethyl)-1H-benzimidazol-2-ylmethyl]-N-[2-(1-naphthyl)ethyl]-1H-benzimidazole-5-carboxamide

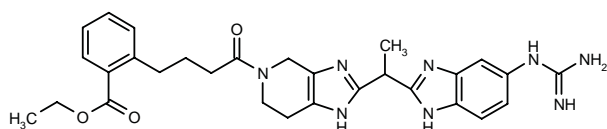


C29 H26 N6 O; Mol wt: 474.5654

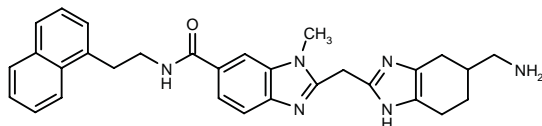
ACTION – Agent for the treatment of inflammatory disorders of the respiratory tract such as asthma and allergic rhinitis, other types of immune-mediated inflammatory disorders such as rheumatoid arthritis, conjunctivitis and inflammatory bowel disease, as well as dermatological disorders and syncytial viral infections, a potent and selective inhibitor of the mast cell protease tryptase. *In vivo* activity was evaluated in an allergic sheep model of asthma, where it produced a significant improvement in airways function in antigen-challenged sheep when administered at a dose of 1 mg as an aerosol formulation. Other compounds from this series of heterobicyclic derivatives include the following:



Compound	R1	R2	R3	R4	Formula
269989	Me	H	H	NHC(=NH)NH ₂	C ₃₀ H ₂₈ N ₈ O
269991	Me	H	H	CH ₂ NH ₂	C ₃₀ H ₂₈ N ₆ O
269993	CH ₂ CH(OH)CH ₂ OH	H	H	NHC(=NH)NH ₂	C ₃₂ H ₃₂ N ₈ O ₃
269994	CH ₂ CH(OH)CH ₂ OH	-O-		NHC(=NH)NH ₂	C ₃₂ H ₃₀ N ₈ O ₄



269990: C29 H34 N8 O3



269992: C30 H32 N6 O

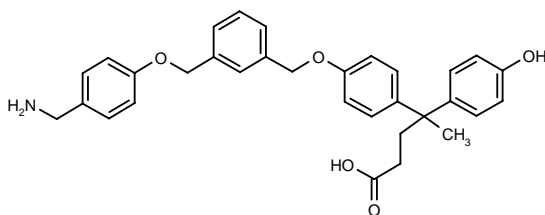
SOURCE – AxyS.

REFERENCES

1. Church, T.J. et al. (AxyS Pharmaceuticals, Inc.) *Cpds. and compsns. for treating diseases associated with serine protease, particularly tryptase, activity.* WO 9845275.

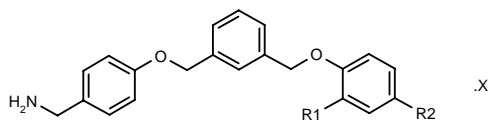
270799

4-[4-[3-[4-(Aminomethyl)phenoxy]benzyloxy]-phenyl]-4-(4-hydroxyphenyl)pentanoic acid



C32 H33 N O5; Mol wt: 511.6147

ACTION – Potent LTB_4 (BLT) receptor antagonist ($K_i = 0.5$ nM) with potential in the treatment of asthma, chronic obstructive pulmonary disorder, chronic bronchitis, arthritis, psoriasis, ulcerative colitis, cystic fibrosis, Alzheimer's disease, shock, ischemia–reperfusion injury, atherosclerosis and multiple sclerosis. A representative compound from a series of benzylamine and phenylethylamine derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
270800	H	4-OH-PhSO ₂	HCl	C ₂₇ H ₂₆ NO ₅ S .HCl
270801	H	4-OH-PhSO	HCl	C ₂₇ H ₂₅ NO ₄ S .HCl
270802	H	4-(α -D-glucopyranosyloxy)-PhC(Me) ₂	HCl	C ₃₈ H ₄₁ NO ₈ .HCl
270803	H	C(Me) ₂ CH ₂ NHCO ₂ Et	fumarate	C ₂₈ H ₃₄ N ₂ O ₄ .C ₄ H ₄ O ₄
270804	H	t-BuO	MeSO ₃ H	C ₂₅ H ₂₉ NO ₃ .CH ₄ O ₃ S
270805	H	4-(1-Pip-CO)-PhC(Me) ₂	H ₂ SO ₄	C ₃₆ H ₄₀ N ₂ O ₃ .H ₂ O ₄ S
270806	OH	4-OH-PhC(Me) ₂		C ₃₀ H ₃₁ NO ₄

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Pharma KG) *New benzylamine and phenylethylamine derivs., process for preparing the same and their use as medicaments.* WO 9849131.

MAb 165-13

270753

ACTION – Monoclonal antibody that binds to the extracellular portion of the α chain of the human IL-5 receptor present on the surface of eosinophils, and inhibits the interaction of IL-5 with its receptor. Potentially useful for the treatment of asthma, allergic disorders and inflammation. Another related antibody is:

MAb 165-5 [270754]

SOURCE – Tanox.

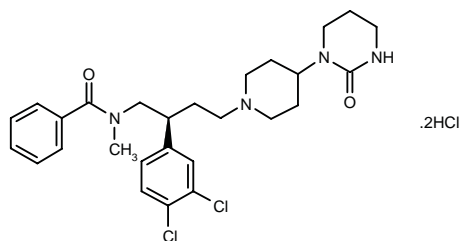
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ZM-274773*

245152

N-[2(S)-(3,4-Dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidin-1-yl]butyl]-*N*-methylbenzamide dihydrochloride



C27 H34 Cl₂ N₄ O₂ . 2HCl; Mol wt: 590.4194

ACTION – Selective tachykinin NK₂ receptor antagonist shown to block the increase in pulmonary resistance induced by esophageal acid in anesthetized guinea pigs at a dose of 10 μ mol/kg.

SOURCE – Zeneca.

REFERENCES

1. Miller, S.C. (Zeneca Ltd.) *Therapeutic heterocycles which antagonize neurokinin receptors.* JP 97501439, US 5567700, WO 9505377.

2. Lengel, D.J. and Rumsey, W.L. *NK1 and NK2 receptor antagonism blocks esophageal acid induced tracheal plasma extravasation and bronchoconstriction.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst W8.

*Identified compound **245152** Drug Data Report 1997, 019(05): 0411.

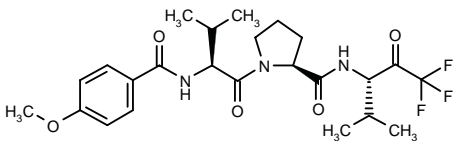
TREATMENT OF RDS AND EMPHYSEMA

ZD-0892*

227831

(4-Methoxybenzoyl-L-valyl-L-prolyl-L-valyl)trifluoromethane

N-(4-Methoxybenzoyl)-L-valyl-N-[3,3,3-trifluoro-1(S)-isopropyl-2-oxopropyl]-L-prolinamide



C24 H32 F3 N3 O5; Mol wt: 499.5268

ACTION – A selective inhibitor of serine elastase ($K_i = 6.7$ nM against human neutrophil elastase; $K_i = 200$ nM against porcine pancreatic elastase) with no inhibitory activity against other serine proteases (trypsin and thrombin), cysteine proteases or matrix metalloproteinases. In hamsters, it inhibited human neutrophil elastase-induced hemorrhage with ED_{50} values of 0.59 and 4.9 mg/kg i.v. and p.o., respectively. In an experimental murine viral myocarditis model, compound administered orally at a dose of 60 mg/kg/day for 15 days reduced myocardial elastase activity and the related coronary microvascular perfusion abnormalities, necrosis, inflammatory cell infiltration, calcification and fibrosis, but had no direct antiviral activity.

SOURCE – Zeneca.

REFERENCES

1. Pegg, S.J. et al. (Zeneca Ltd.) *Diastereomeric pure trifluoromethyl ketone peptide derivs. as inhibitors of human leukocyte elastase*. EP 743953, JP 97508902, US 5739157, WO 9521855.

2. Edwards, P.D. et al. *Discovery and biological activity of orally active peptidyl trifluoromethyl ketone inhibitors of human neutrophil elastase*. J Med Chem 1997, 40(12): 1876.

3. Huang, Y.-I. et al. *Effect of trifluoromethyl ketone-based elastase inhibitors on neutrophil function in vitro*. J Leukocyte Biol 1998, 64(3): 322.

4. Lee, J.K. et al. *A serine elastase inhibitor reduces inflammation and fibrosis and preserves cardiac function after experimentally-induced murine myocarditis*. Nat Med 1998, 4(12): 1383.

5. Veale, C.A. et al. *Orally active trifluoromethyl ketone inhibitors of human leukocyte elastase*. J Med Chem 1997, 40(20): 3173.

6. 87 development projects under way at Zeneca. Prous Science Daily Essentials 1997, Dec 16.

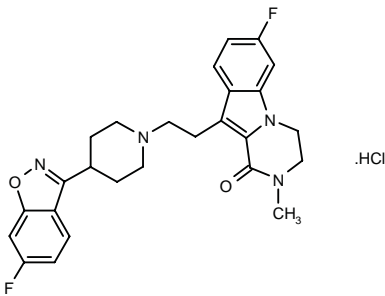
*Identified compound 227831 Drug Data Report 1996, 018(01): 0040.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

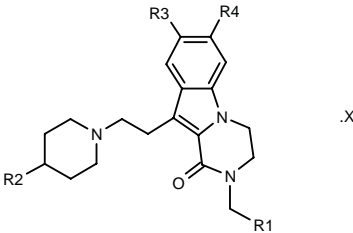
269814

7-Fluoro-10-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-one hydrochloride



C26 H26 F2 N4 O2 . HCl; Mol wt: 500.9743

ACTION – 5-HT₂ receptor antagonist, as shown in a binding assay using [³H]-spiroperidol as the ligand and rat cerebral cortex preparations ($IC_{50} < 1$ μM), and 5-HT₁-like receptor antagonist, as demonstrated in dog saphenous vein. Potentially useful in the treatment or prevention of various types of hypertension, heart failure, myocardial infarction, angina, coronary or peripheral vasospasm, thrombosis, restenosis following angioplasty and pathological conditions associated with atherosclerosis, microcirculatory disturbances and pulmonary dysfunction. Within this series of dihydropyrazino[1,2-a]indol-1-one derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
269815	CONH2	6-F-3-benzisoxazolyl	H	F	HCl	C ₂₇ H ₂₇ F ₂ N ₅ O ₃ .HCl
269817	H	4-F-PhCO	H	F	HCl	C ₂₆ H ₂₇ F ₂ N ₃ O ₂ .HCl
269818	CH2OH	4-F-PhCO	F	H	HCl	C ₂₇ H ₂₆ F ₂ N ₃ O ₃ .HCl
269816	CONH2	6-F-1-Me-3-indazolyl	F	H	2HCl	C ₂₇ H ₂₆ F ₂ N ₇ O ₂ .2HCl
269819	CH2OH	6-F-3-benzisothiazolyl	F	H	HCl	C ₂₆ H ₂₇ F ₂ N ₅ O ₂ S.HCl
269820	1-Piz-CO	6-F-3-benzisothiazolyl	F	H	3HCl	C ₃₀ H ₃₃ F ₂ N ₇ O ₂ S.3HCl
269821	-CO-L-Pro-OH	6-F-3-benzisothiazolyl	F	H	2HCl	C ₃₁ H ₃₂ F ₂ N ₆ O ₄ S.2HCl
269822	CH2CH2NH-C(=NH)NH2	6-F-3-benzisothiazolyl	F	H	3HCl	C ₂₈ H ₃₂ F ₂ N ₆ OS.3HCl

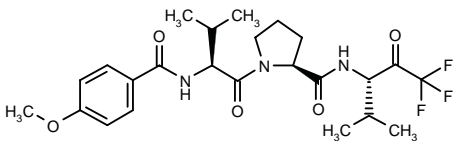
TREATMENT OF RDS AND EMPHYSEMA

ZD-0892*

227831

(4-Methoxybenzoyl-L-valyl-L-prolyl-L-valyl)trifluoromethane

N-(4-Methoxybenzoyl)-L-valyl-N-[3,3,3-trifluoro-1(S)-isopropyl-2-oxopropyl]-L-prolinamide



C24 H32 F3 N3 O5; Mol wt: 499.5268

ACTION – A selective inhibitor of serine elastase ($K_i = 6.7$ nM against human neutrophil elastase; $K_i = 200$ nM against porcine pancreatic elastase) with no inhibitory activity against other serine proteases (trypsin and thrombin), cysteine proteases or matrix metalloproteinases. In hamsters, it inhibited human neutrophil elastase-induced hemorrhage with ED_{50} values of 0.59 and 4.9 mg/kg i.v. and p.o., respectively. In an experimental murine viral myocarditis model, compound administered orally at a dose of 60 mg/kg/day for 15 days reduced myocardial elastase activity and the related coronary microvascular perfusion abnormalities, necrosis, inflammatory cell infiltration, calcification and fibrosis, but had no direct antiviral activity.

SOURCE – Zeneca.

REFERENCES

1. Pegg, S.J. et al. (Zeneca Ltd.) *Diastereomeric pure trifluoromethyl ketone peptide derivs. as inhibitors of human leukocyte elastase*. EP 743953, JP 97508902, US 5739157, WO 9521855.

2. Edwards, P.D. et al. *Discovery and biological activity of orally active peptidyl trifluoromethyl ketone inhibitors of human neutrophil elastase*. J Med Chem 1997, 40(12): 1876.

3. Huang, Y.-I. et al. *Effect of trifluoromethyl ketone-based elastase inhibitors on neutrophil function in vitro*. J Leukocyte Biol 1998, 64(3): 322.

4. Lee, J.K. et al. *A serine elastase inhibitor reduces inflammation and fibrosis and preserves cardiac function after experimentally-induced murine myocarditis*. Nat Med 1998, 4(12): 1383.

5. Veale, C.A. et al. *Orally active trifluoromethyl ketone inhibitors of human leukocyte elastase*. J Med Chem 1997, 40(20): 3173.

6. 87 development projects under way at Zeneca. Prous Science Daily Essentials 1997, Dec 16.

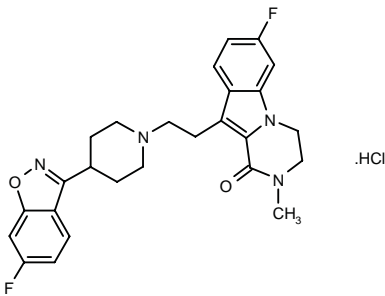
*Identified compound 227831 Drug Data Report 1996, 018(01): 0040.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

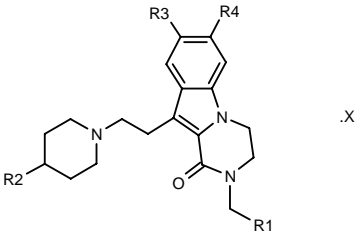
269814

7-Fluoro-10-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-one hydrochloride



C26 H26 F2 N4 O2 . HCl; Mol wt: 500.9743

ACTION – 5-HT₂ receptor antagonist, as shown in a binding assay using [³H]-spiroperidol as the ligand and rat cerebral cortex preparations ($IC_{50} < 1$ μ M), and 5-HT₁-like receptor antagonist, as demonstrated in dog saphenous vein. Potentially useful in the treatment or prevention of various types of hypertension, heart failure, myocardial infarction, angina, coronary or peripheral vasospasm, thrombosis, restenosis following angioplasty and pathological conditions associated with atherosclerosis, microcirculatory disturbances and pulmonary dysfunction. Within this series of dihydropyrazino[1,2-a]indol-1-one derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
269815	CONH2	6-F-3-benzisoxazolyl	H	F	HCl	C ₂₇ H ₂₇ F ₂ N ₅ O ₃ .HCl
269817	H	4-F-PhCO	H	F	HCl	C ₂₆ H ₂₇ F ₂ N ₃ O ₂ .HCl
269818	CH2OH	4-F-PhCO	F	H	HCl	C ₂₇ H ₂₆ F ₂ N ₃ O ₃ .HCl
269816	CONH2	6-F-1-Me-3-indazolyl	F	H	2HCl	C ₂₇ H ₂₆ F ₂ N ₇ O ₂ .2HCl
269819	CH2OH	6-F-3-benzisothiazolyl	F	H	HCl	C ₂₆ H ₂₇ F ₂ N ₅ O ₂ S.HCl
269820	1-Piz-CO	6-F-3-benzisothiazolyl	F	H	3HCl	C ₃₀ H ₃₃ F ₂ N ₇ O ₂ S.3HCl
269821	-CO-L-Pro-OH	6-F-3-benzisothiazolyl	F	H	2HCl	C ₃₁ H ₃₂ F ₂ N ₆ O ₄ S.2HCl
269822	CH2CH2NH-C(=NH)NH2	6-F-3-benzisothiazolyl	F	H	3HCl	C ₂₈ H ₃₂ F ₂ N ₆ OS.3HCl

SOURCE – Synthélabo.

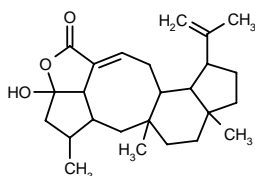
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S-19777

270969

2a-Hydroxy-7-isopropenyl-1,9a,11a-trimethylperhydro-3-oxapentaleno[1',6':4,5,6]cycloocta[1,2-e]inden-4-one



C25 H36 O3; Mol wt: 384.5564

ACTION – Endothelin antagonist isolated from *Emericella aurantiobrunnea* SANK 19777 (FERM BP-5917), with affinity for both ET_A and ET_B receptors (IC₅₀ = 76.5 and 68.3 μM, respectively).

SOURCE – Sankyo.

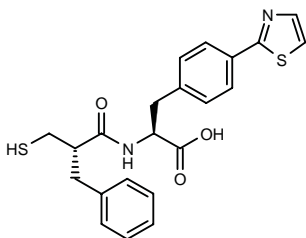
REFERENCES

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Z-13752A*

264479

N-[2(S)-Benzyl-3-sulfanylpropanoyl]-4-(2-thiazolyl)-L-phenylalanine



C22 H22 N2 O3 S2; Mol wt: 426.5588

ACTION – Dual inhibitor of angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP), giving IC₅₀ values of 3.2 nM (captopril IC₅₀ = 4.6 nM) for inhibition of rat lung ACE and of 1.8 nM (SQ-28603 IC₅₀ = 5.4 nM) for inhibition of rat renal NEP; compound did not interact with other proteases, α- and β-adrenoceptors, histamine, dopamine, 5-HT, angiotensin AT₁ or ET_A receptors at concentrations of up to 10 μM. In an *ex vivo* model in spontaneous hypertensive rats (SHR), it strongly reduced lung ACE (ED₅₀ = 3.2 μmol/kg i.v.) and renal NEP (ED₅₀ = 1.5 μmol/kg i.v.). In *in vivo* in SHR, it was as effective as captopril in reducing systolic blood pressure (30-40 mmHg at 100 μmol/kg b.i.d. for 5 days). In DOCA/salt-treated rats, compound at a dose of 10 μmol/kg i.v. significantly reduced blood pressure, without affecting heart rate, whereas captopril did not reduce blood pressure at up to 300 μmol/kg. Z-13752A also provided protection against arrhythmias, mortality and S-T segment elevation in a model of myocardial ischemia in dogs.

SOURCE – Zambon.

REFERENCES

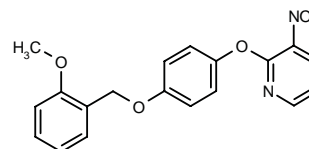
1. Santangelo, F. et al. (Zambon Group SpA) *Thiol derivs. with metallopeptidase inhibitory activity*. US 5760241.
2. Macchi, F. et al. *Determination of the new dual ACE-NEP inhibitor Z13752A in human plasma by HPLC with fluorescence detection*. Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 172.
3. Morazzoni, G. et al. *Dual inhibition of ACE and NEP activities induced by i.v. and oral administration of Z13752A in spontaneously hypertensive rats*. Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 138.
4. Morazzoni, G. et al. *In vitro and ex vivo characterization of Z13752A, a new dual-acting ACE/NEP inhibitor*. Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 139.
5. Pradella, L. et al. *Z13752A, a new potent dual angiotensin converting enzyme and neutral endopeptidase inhibitor produces antihypertensive effect in SHR rats and DOCA salt hypertensive rats*. Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 141.
6. Rastigar, M.A. et al. *Does inhibition of bradykinin catabolism modify the severity of arrhythmias in myocardial ischaemia?* J Mol Cell Cardiol 1998, Abst 15.

*Identified compound **264479** Drug Data Report 1998, 020(07): 0581.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

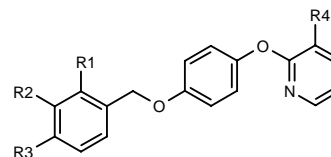
269652

2-[4-(2-Methoxybenzyloxy)phenoxy]-3-nitropyridine



C19 H16 N2 O5; Mol wt: 352.3444

ACTION – Cardiac, cerebral and renal antiischemic agent, an inhibitor of Na⁺/Ca²⁺ exchange from a series of phenoxypyridine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
269653	H	H	Cl	NO2	C ₁₈ H ₁₃ ClN ₂ O ₄
269654	H	H	CF ₃	NO2	C ₁₉ H ₁₃ F ₃ N ₂ O ₄
269655	H	Br	H	NO2	C ₁₈ H ₁₃ BrN ₂ O ₄
269656	H	H	Br	NO2	C ₁₈ H ₁₃ BrN ₂ O ₄
269657	H	H	F	NO2	C ₁₈ H ₁₃ FN ₂ O ₄
269658	H	H	CN	NO2	C ₁₉ H ₁₃ N ₃ O ₄
269659	Me	H	H	NH2	C ₁₉ H ₁₈ N ₂ O ₂

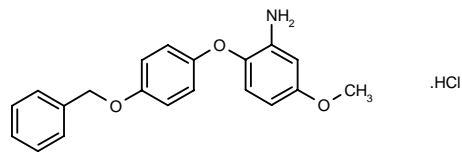
SOURCE – Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Phenoxypyridine derivs*. JP 98265460.

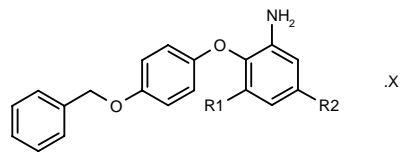
269845

2-(4-Benzyloxyphenoxy)-5-methoxyaniline hydrochloride



C20 H19 N O3 . HCl; Mol wt: 357.835

ACTION – Agent for the treatment of cardiac, cerebral and renal ischemic disorders that acts by inhibiting Na⁺/Ca²⁺ exchange (IC₅₀ = 1.1 μM). A representative compound from a series of 2-phenoxyaniline derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
269846	NH2	H	2HCl	C ₁₉ H ₁₈ N ₂ O ₂ ·2HCl
269847	H	OEt	HCl	C ₂₁ H ₂₁ NO ₃ ·HCl
269848	H	OCH2CONH2	HCl	C ₂₁ H ₂₀ N ₂ O ₄ ·HCl
269849	H	OCH2CO2Me	HCl	C ₂₂ H ₂₁ NO ₅ ·HCl

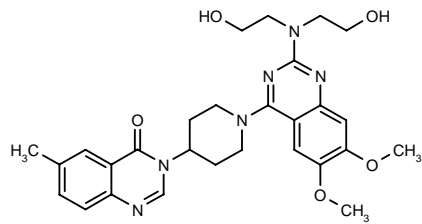
SOURCE – Taisho.

REFERENCES

1. Ota, T. et al. (Taisho Pharmaceutical Co., Ltd.) 2-Phenoxyaniline derivs. JP 98324669, WO 9843943.

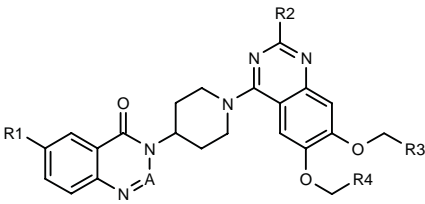
270374

3-[1-[2-[N,N-Bis(2-hydroxyethyl)amino]-6,7-dimethoxy-4-quinazolinyl]-4-piperidinyl]-6-methyl-4(3H)-quinazolinone

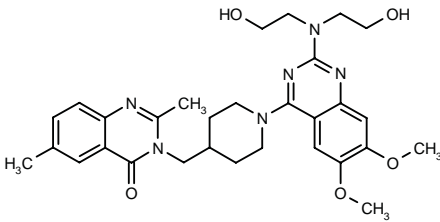


C28 H34 N6 O5; Mol wt: 534.6136

ACTION – Adenosine reuptake inhibitor, as demonstrated by inhibition of [³H]-adenosine uptake in human erythrocytes (IC₅₀ = 14 nM). Additionally, compound inhibited [³H]-NBI binding in guinea pig cerebral cortex homogenates with a K_i value of 8.3 nM. Potentially useful for the treatment or prevention of inflammation and as a cardioprotective agent. Other compounds from this series of piperidine derivatives include the following:



Compound	R1	R2	R3=R4	A	Formula
270375	Me	H	H	CH	C ₂₄ H ₂₅ N ₅ O ₃
270376	Ac	H	H	CH	C ₂₅ H ₂₅ N ₅ O ₄
270377	Me	H	H	N	C ₂₃ H ₂₄ N ₆ O ₃
270379	Me	H	Me	CH	C ₂₆ H ₂₉ N ₅ O ₃
270380	Br	4-morpholinyl	Me	CH	C ₂₉ H ₃₃ BrN ₆ O ₄
270381	Me	H	Me	C(Ph)	C ₃₂ H ₃₃ N ₅ O ₃



270378: C30 H38 N6 O5

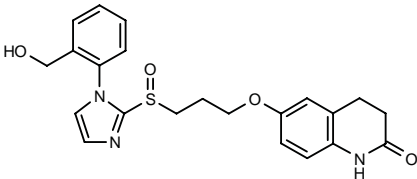
SOURCE – Kyowa Hakko.

REFERENCES

1. Fujiwara, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) Piperidine derivs. WO 9833792.

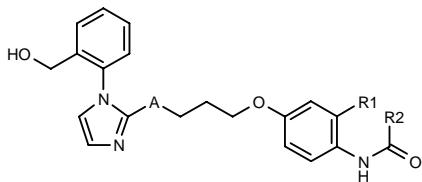
270415

6-[3-[1-[2-(Hydroxymethyl)phenyl]-1H-imidazol-2-ylsulfanyl]propoxy]-1,2,3,4-tetrahydro-2-quinolinone



C22 H23 N3 O4 S; Mol wt: 425.5067

ACTION – Agent for the treatment of arteriosclerosis and thrombotic disorders that acts by inhibiting platelet adhesion and the production of 12-hydroxyeicosatetraenoic acid (12-HETE; IC₅₀ = 0.07 μM in collagen-stimulated human platelets). Other specifically claimed compounds from this series of carbostyryl derivatives include the following:



Compound	R1,R2	A	Isomer	Formula
270416	-(CH2)2-	SO	S-(+)	C ₂₂ H ₂₃ N ₃ O ₄ S
270417	-(CH2)2-	SO	R-(-)	C ₂₂ H ₂₃ N ₃ O ₄ S
270418	-CH=CH-	SO ₂		C ₂₂ H ₂₁ N ₃ O ₅ S
270419	-CH=CH-	SO		C ₂₂ H ₂₁ N ₃ O ₄ S
270420	-CH=CH-	SO	S-(+)	C ₂₂ H ₂₁ N ₃ O ₄ S
270421	-CH=CH-	SO	R-(-)	C ₂₂ H ₂₁ N ₃ O ₄ S
270422	-CH(OH)CH ₂ -	SO		C ₂₂ H ₂₃ N ₃ O ₅ S
270423	-CH ₂ CH(OH)-	SO ₂		C ₂₂ H ₂₃ N ₃ O ₆ S

SOURCE – Otsuka.

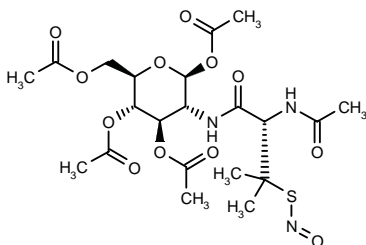
REFERENCES

1. Ohtani, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Novel carbostyryl deriv.* JP 99001482, WO 9846593.

RIG-200

269234

2-(*N*-Acetyl-*S*-nitroso-*D*-penicillamido)-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranose



C21 H31 N3 O12 S; Mol wt: 549.5509

ACTION – Slow-release nitric oxide (NO) donor that exhibits transient vasodilating activity in endothelium-intact rat femoral arteries, similar to sodium nitroprusside, and a sustained effect for over 4 h in endothelium-denuded vessels, contrary to reference compound. In humans, it exhibits comparable local vasodilating activity to sodium nitroprusside following local infusion in the dorsal hand vein of healthy male volunteers. Potentially useful in the treatment of cardiovascular disorders involving endothelial damage, such as in preventing restenosis following percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG).

SOURCE – University of St. Andrews, St. Andrews (GB).

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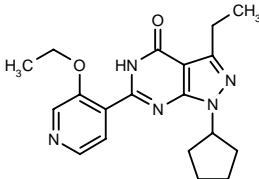
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WIN-65579

268693

1-Cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



C19 H23 N5 O2; Mol wt: 353.4237

ACTION – Potent phosphodiesterase type 5 (PDE5) inhibitor with IC₅₀ values of 2-3 nM against enzyme from human or canine vessels; it has low activity against PDE1, PDE2 and PDE3 (IC₅₀ > 3 μM) and it shows moderate inhibitory activity against PDE4 (IC₅₀ approx. 100 nM). Compound induces endothelium-dependent relaxation of rat aortic smooth muscle (EC₅₀ = 60 nM) and decreases mean arterial blood pressure when administered at a dose of 10 mg/kg i.v. (40 ± 7 mmHg) or p.o. (24 ± 3 mmHg) to conscious spontaneously hypertensive rats, with slight or no significant effect on heart rate. It restored the blood pressure-reducing effect of nitroglycerin in conscious nitroglycerin-tolerant rats. Potentially useful in the treatment of angina, pulmonary hypertension, impotence, acute respiratory distress syndrome and in cases of nitroglycerin tolerance.

SOURCE – Sterling-Winthrop.

REFERENCES

1. Bacon, E.R. et al. (Sanofi Winthrop) *6-Heterocyclyl pyrazolo[3,4-d]pyrimidin-4-ones and compsns. and method of use.* US 5294612.

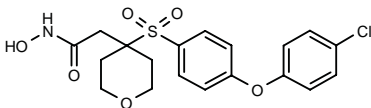
2. Silver, P.J. et al. *Cardiovascular activity of WIN 65579, a novel inhibitor of cyclic GMP phosphodiesterase 5.* Eur J Pharmacol 1998, 349(2-3): 263.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

RS-113456

269834

4-[4-(4-Chlorophenoxy)phenylsulfonyl]-*N*-hydroxy-tetrahydro-2*H*-pyran-4-acetamide



C19 H20 Cl N O6 S; Mol wt: 425.887

ACTION – Specific, nonselective, competitive matrix metalloproteinase (MMP) inhibitor with *in vitro* activity against 8 human and 3 rat MMP subtypes (K_i = 0.054-240.0 nmol/l against human collagenase 1, 2 and 3, gelatinase A and B, stromelysin 1, matrilysin and metalloelastase; K_i = 0.099-4.2 nmol/l against rat collagenase 3, gelatinase A and stromelysin 1). In a rodent cartilage sponge degradation model, it inhibited MMPs after oral administration. Compound inhibited flow-mediated arterial enlargement in a rat common femoral arteriovenous fistula model in the dose range of 25-75 mg/kg p.o., without apparent hemodynamic effects. Potentially useful for preventing abdominal aortic aneurysms.

SOURCE – Roche Bioscience.

REFERENCES

1. Bender, S.L. et al. (F. Hoffmann-La Roche AG; Agouron Pharmaceuticals, Inc.) *Matrix metalloprotease inhibitors*. EP 780386.

2. Abbruzzese, T.A. et al. *Matrix metalloproteinase inhibition limits enlargement in a rodent arteriovenous fistula model*. Surgery 1998, 124(2): 328.

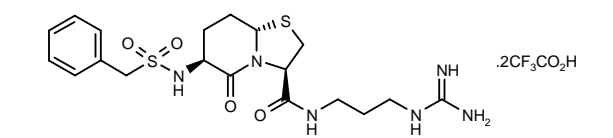
3. Karkowski, J.K. et al. *Dose-dependent limitation of chronic arterial enlargement by the matrix metalloproteinase inhibitor RS-113,456*. Circulation 1998, 98(17, Suppl.): Abst 4242.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

268332

(3*R*,6*S*,8*aS*)-6-(Benzylsulfonamido)-*N*-[3-(carbamimidoyl)propyl]-5-oxohexahydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxamide bis(trifluoroacetate)



C19 H28 N6 O4 S2 . 2 C2 H F3 O2; Mol wt: 696.644

Colorless oil.

ACTION – Selective, noncovalent thrombin inhibitor with high affinity for the enzyme (K_i = 111 nM), 70-fold selectivity over trypsin and no activity against plasmin.

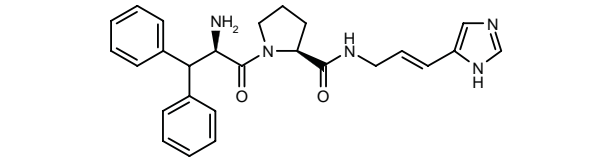
SOURCE – Novartis.

REFERENCES

1. Wagner, J. et al. *Rational design, synthesis, and X-ray structure of selective noncovalent thrombin inhibitors*. J Med Chem 1998, 41(19): 3664.

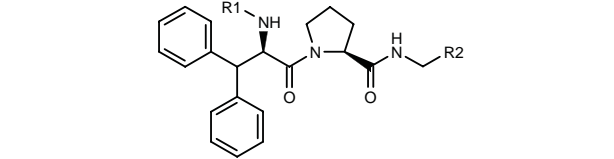
269688

3,3-Diphenyl-D-alanyl-L-proline 3-(1*H*-imidazol-5-yl)-2(*E*)-propenylamide

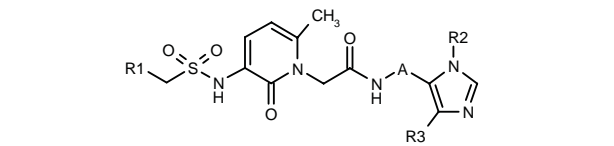


C26 H29 N5 O2; Mol wt: 443.5481

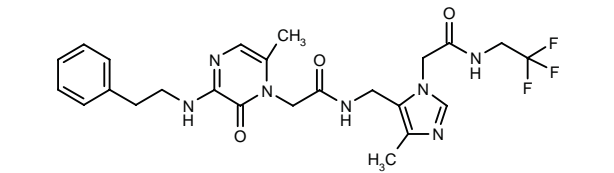
ACTION – Platelet aggregation inhibitor that acts by inhibiting thrombin. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	Formula
269689	SO2CH2Ph	5-imidazolyl-CH2CH2	C33H37N5O4S
269690	(1 <i>S</i> ,4 <i>S</i>)-7,7-(Me)2-2-oxo-bicyclo[2.2.1]hept-1-yl-CH2SO2	5-imidazolyl-CH=CH	C36H43N5O5S
269696	H	2-NH2-4-thiazolyl-CH=CH	C26H29N5O2S



Compound	R1	R2	R3	A	Formula
269691	Ph	H	H	-(CH2)3-	C21H25N5O4S
269692	Ph	CH2CO2H	Me	-CH2-	C22H25N5O6S
269693	Ph	t-BuCH2NHCOCH2	Me	-CH2-	C27H36N6O5S
269695	Bu	3-Pip-NHCOCH2	Me	-CH2-	C25H39N7O5S



269694: C24 H28 F3 N7 O3

SOURCE – Merck & Co.

REFERENCES

1. Isaacs, R.C.A. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 9842342.

ACTION – Specific, nonselective, competitive matrix metalloproteinase (MMP) inhibitor with *in vitro* activity against 8 human and 3 rat MMP subtypes (K_i = 0.054-240.0 nmol/l against human collagenase 1, 2 and 3, gelatinase A and B, stromelysin 1, matrilysin and metalloelastase; K_i = 0.099-4.2 nmol/l against rat collagenase 3, gelatinase A and stromelysin 1). In a rodent cartilage sponge degradation model, it inhibited MMPs after oral administration. Compound inhibited flow-mediated arterial enlargement in a rat common femoral arteriovenous fistula model in the dose range of 25-75 mg/kg p.o., without apparent hemodynamic effects. Potentially useful for preventing abdominal aortic aneurysms.

SOURCE – Roche Bioscience.

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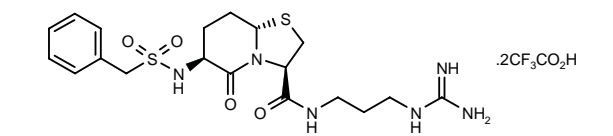
3. Karkowski, J.K. et al. *Dose-dependent limitation of chronic arterial enlargement by the matrix metalloproteinase inhibitor RS-113,456*. Circulation 1998, 98(17, Suppl.): Abst 4242.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

268332

(3*R*,6*S*,8*aS*)-6-(Benzylsulfonamido)-*N*-[3-(carbamimidoyl)propyl]-5-oxohexahydro-5*H*-thiazolo[3,2-*a*]-pyridine-3-carboxamide bis(trifluoroacetate)



C19 H28 N6 O4 S2 . 2 C2 H F3 O2; Mol wt: 696.644

Colorless oil.

ACTION – Selective, noncovalent thrombin inhibitor with high affinity for the enzyme (K_i = 111 nM), 70-fold selectivity over trypsin and no activity against plasmin.

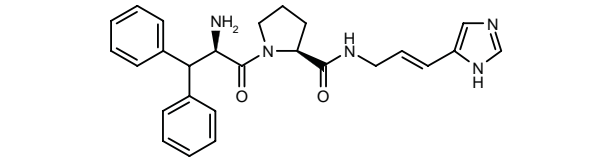
SOURCE – Novartis.

REFERENCES

1. Wagner, J. et al. *Rational design, synthesis, and X-ray structure of selective noncovalent thrombin inhibitors*. J Med Chem 1998, 41(19): 3664.

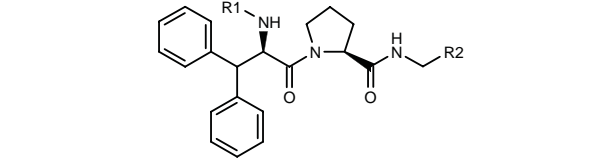
269688

3,3-Diphenyl-D-alanyl-L-proline 3-(1*H*-imidazol-5-yl)-2(*E*)-propenylamide

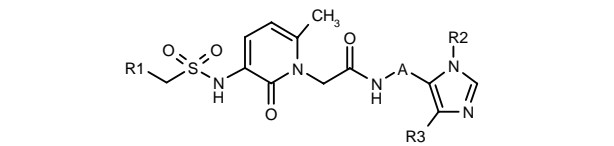


C26 H29 N5 O2; Mol wt: 443.5481

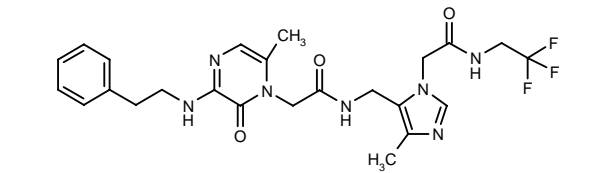
ACTION – Platelet aggregation inhibitor that acts by inhibiting thrombin. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	Formula
269689	SO2CH2Ph	5-imidazolyl-CH2CH2	C33H37N5O4S
269690	(1 <i>S</i> ,4 <i>S</i>)-7,7-(Me)2-2-oxo-bicyclo[2.2.1]hept-1-yl-CH2SO2	5-imidazolyl-CH=CH	C36H43N5O5S
269696	H	2-NH2-4-thiazolyl-CH=CH	C26H29N5O2S



Compound	R1	R2	R3	A	Formula
269691	Ph	H	H	-(CH2)3-	C21H25N5O4S
269692	Ph	CH2CO2H	Me	-CH2-	C22H25N5O6S
269693	Ph	t-BuCH2NHCOCH2	Me	-CH2-	C27H36N6O5S
269695	Bu	3-Pip-NHCOCH2	Me	-CH2-	C25H39N7O5S



269694: C24 H28 F3 N7 O3

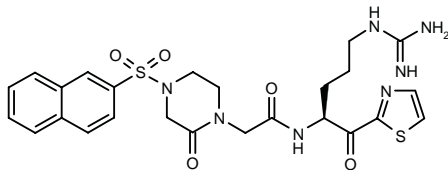
SOURCE – Merck & Co.

REFERENCES

1. Isaacs, R.C.A. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 9842342.

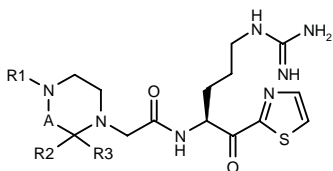
270455

N-[4-Guanidino-2(*S*)-(2-thiazolylcarbonyl)butyl]-2-[4-(2-naphthylsulfonyl)-2-oxopiperazin-1-yl]acetamide

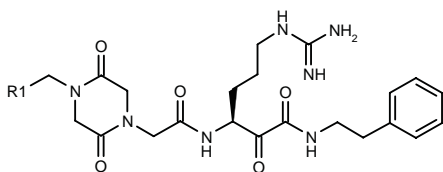


C₂₅ H₂₉ N₇ O₅ S₂; Mol wt: 571.6801

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa. A representative compound from a series of piperazine derivatives, wherein the following are also included:



Compound	R1	R2	R3	A	Formula
270456	SO ₂ CH ₂ Ph	-O-	-CH ₂ -	-CH ₂ -	C ₂₂ H ₂₉ N ₇ O ₅ S ₂
270457	SO ₂ CH=CHPh	-O-	-CH ₂ -	-CH ₂ -	C ₂₃ H ₂₉ N ₇ O ₅ S ₂
270458	4-Pip-CH ₂ CH ₂	H	H	-CH ₂ -	C ₂₂ H ₃₈ N ₈ O ₂ S
270459	SO ₂ CH ₂ Ph	-O-	-(CH ₂) ₂ -	-(CH ₂) ₂ -	C ₂₃ H ₃₁ N ₇ O ₅ S ₂



Compound	R1	Formula
270460	4-Pip-CH ₂	C ₂₈ H ₄₂ N ₈ O ₅
270461	1-[NH ₂ C(=NH)]-4-Pip-CH ₂	C ₂₉ H ₄₄ N ₁₀ O ₅
270462	4-Pip	C ₂₇ H ₄₀ N ₈ O ₅

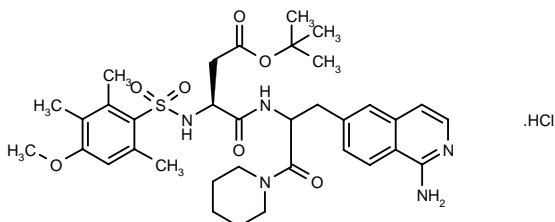
SOURCE – COR Therapeutics.

REFERENCES

1. Marlowe, C.K. et al. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. WO 9846591.

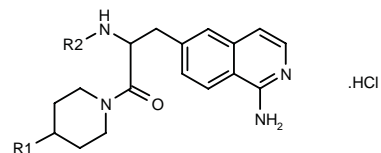
270623

N-[1-(1-Amino-6-isoquinolylmethyl)-2-oxo-2-(1-piperidinylethyl)-3(*S*)-(4-methoxy-2,3,6-trimethylphenylsulfonylamido)succinamic acid *tert*-butyl ester hydrochloride

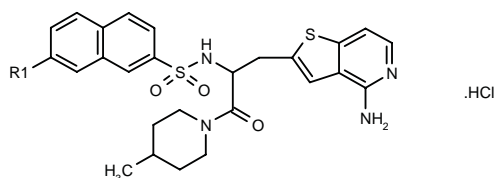


C₃₅ H₄₇ N₅ O₇ S . HCl; Mol wt: 718.3112

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human thrombin (IC₅₀ = 0.082 μM) reported to possess greatly improved oral bioavailability as compared to structurally related compounds by virtue of the presence of an aminoquinoline or related group as the basic moiety. Other compounds from this series of antithrombotic agents with improved oral absorption include the following:



Compound	R1	R2	Formula
270626	H	2,2,5,7,8-(Me)5-3,4-dihydro-2H-1-benzopyran-6-yl-SO ₂ NHNHCO	C ₃₂ H ₄₂ N ₆ O ₅ S.HCl
270628	Me	2-Naph-SO ₂	C ₂₈ H ₃₀ N ₄ O ₃ S.HCl



Compound	R1	Formula
270629	H	C ₂₆ H ₂₈ N ₄ O ₃ S ₂ .HCl
270631	OMe	C ₂₇ H ₃₀ N ₄ O ₄ S ₂ .HCl

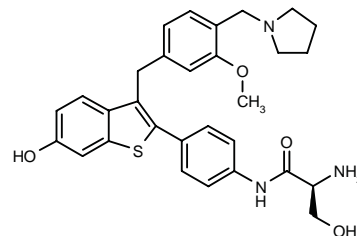
SOURCE – Akzo Nobel.

REFERENCES

1. Van Boeckel, C.A.A. et al. (Akzo Nobel N.V.) *Heterocyclic derivs. and their use as antithrombotic agents*. WO 9847876.

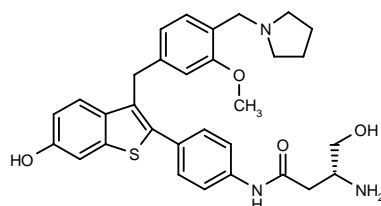
270833

*N*¹-[4-[6-Hydroxy-3-[3-methoxy-4-(1-pyrrolidinylmethyl)-benzyl]benzo[*b*]thiophen-2-yl]phenyl]-L-serinamide



C₃₀ H₃₃ N₃ O₄ S; Mol wt: 531.6737

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of human thrombin. Another specifically claimed compound from this series of benzo[*b*]thiophene derivatives is:



270834: C₃₁ H₃₅ N₃ O₄ S

SOURCE – Lilly.

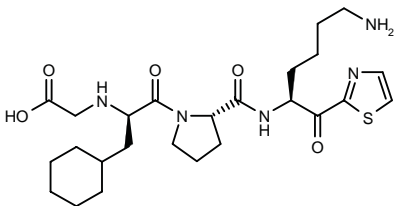
REFERENCES

1. Chirgadze, N.Y. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9848794.

ORG-37432

267803

N-(Carboxymethyl)-3-cyclohexyl-D-alanyl-N-[5-amino-1(S)-(2-thiazolylcarbonyl)pentyl]-L-prolinamide



C25 H39 N5 O5 S; Mol wt: 521.6791

ACTION – Orally active thrombin inhibitor (IC₅₀ = 0.16 μM) with good antithrombotic potency in a rat arterial thrombosis model (ED₅₀ = 19 nmol/kg/min i.v.). Compound showed good oral bioavailability in both rats (23%) and dogs (38%).

SOURCE – Organon.

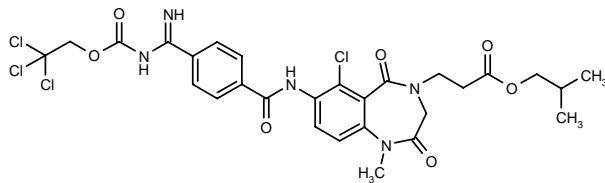
REFERENCES

1. Adang, A.E.P. et al. (Akzo Nobel N.V.) *Thrombin inhibitors*. EP 858464, WO 9717363.
2. Adang, A.E.P. et al. *A polar pharmacophore for oral bioavailability in thrombin inhibitors*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.157.

ANTIPLATELET THERAPY

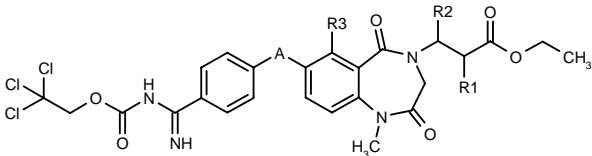
270060

3-[6-Chloro-1-methyl-2,5-dioxo-7-[4-[N¹-(2,2,2-trichloroethoxycarbonyl)amidino]benzamido]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-4-yl]propionic acid iso-butyl ester



C28 H29 Cl4 N5 O7; Mol wt: 689.3771

ACTION – Trichloroethoxycarbonyl prodrug of the known fibrinogen receptor antagonist G-7464*, reported to exhibit greatly improved oral bioavailability relative to the ethoxycarbonyl prodrug. Other compounds within this series of haloalkoxycarbonyl prodrugs of pharmaceutical agents containing basic or polar nitrogen-containing functionalities, particularly fibrinogen antagonists and thrombin, trypsin and factor Xa inhibitors, include the following:



Compound	R1	R2	R3	A	Formula
270061	H	Me	Cl	-CONH-	C ₂₇ H ₂₇ Cl ₄ N ₅ O ₇
270062	H	H	H	-ethynylene-	C ₂₇ H ₂₅ Cl ₃ N ₄ O ₆
270063	H	H	H	-CH ₂ O-	C ₂₈ H ₂₉ Cl ₄ N ₅ O ₇
270064	Me	H	Cl	-CONH-	C ₂₇ H ₂₇ Cl ₄ N ₅ O ₇

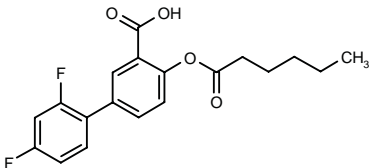
SOURCE – Genentech.

REFERENCES

1. Blackburn, B. et al. (Genentech, Inc.) *Halo-alkoxycarbonyl prodrugs*. WO 9846576.
*See G-7570 Drug Data Rep 1996, 018(10): 0904.

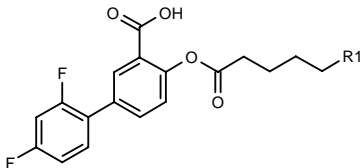
270323

2',4'-Difluoro-4-(hexanoyloxy)biphenyl-3-carboxylic acid



C19 H18 F2 O4; Mol wt: 348.3432

ACTION – Platelet aggregation inhibitor, a novel diflunisal ester with additional radical-scavenging activity, enhanced hepatic clearance and low ulcerogenic potential. Other representative compounds within this series of diflunisal esters include the following:



Compound	R1	Formula
270324	H	C ₁₈ H ₁₆ F ₂ O ₄
270325	Et	C ₂₀ H ₂₀ F ₂ O ₄

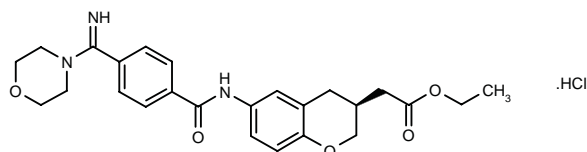
SOURCE – University of Queensland, St. Lucia (AU).

REFERENCES

1. Yung-Yu Hung, D. and Roberts, M.S. (University of Queensland) *Novel diflunisal esters and related cpds*. WO 9846234.

MS-180¹⁻⁶**248804**

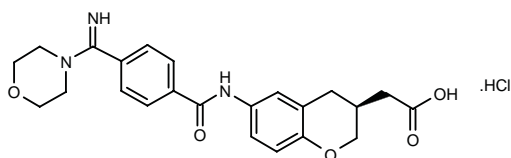
(–)-2-[6-[4-(4-Morpholinylcarbonimidoyl)benzamido]-3,4-dihydro-2H-1-benzopyran-3(S)-yl]acetic acid ethyl ester hydrochloride



C₂₅ H₂₉ N₃ O₅ . HCl; Mol wt: 487.981

Pale yellow solid, m.p. 242-4 °C, $[\alpha]_D^{20}$ –14.5° (c 1.0, MeOH).

ACTION – Orally active antiplatelet agent, a prodrug of **MS-28168**, a potent fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 0.12 nM) and platelet aggregation inhibitor (IC₅₀ = 44 nM against ADP-induced human platelet aggregation). After oral administration, compound dose-dependently inhibited *ex vivo* ADP-induced platelet aggregation in dogs at doses of 1-10 mg/kg (60, 85 and 100% inhibition, respectively, at 1, 3 and 10 mg/kg), and it inhibited thrombus formation in a guinea pig arteriovenous shunt model, being 200 and 50 times more potent than ticlopidine and aspirin, respectively. Selected as a candidate for clinical evaluation in the treatment of thrombosis.



MS-28168^{*1,3,5} [250099]: C₂₃ H₂₅ N₃ O₅ . HCl

SOURCE – Mitsui Chemicals.

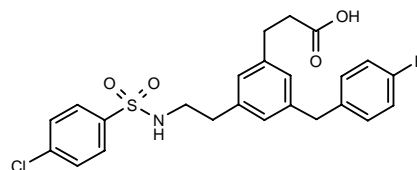
REFERENCES

1. Yamashita, H. et al. (Mitsui Chemicals, Inc.) *Amidine derivs. and platelet aggregation inhibitor containing the same*. EP 760364, JP 97124581, US 5719145.
2. Kawazura, H. et al. *Antithrombotic effect of MS-180, an orally active GPIIb/IIIa antagonist, on arterial thrombosis model in guinea-pigs*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-173.
3. Okumura, K. et al. *New platelet fibrinogen receptor glycoprotein IIb-IIIa antagonists: Orally active series of N-alkylated amidines with a 6,6-bicyclic template*. J Med Chem 1998, 41(21): 4036.
4. Yamashita, H. et al. *New oral fibrinogen antagonist*. 117th Annu Meet Pharm Soc Jpn (March 26-28, Tokyo) 1997, Abst 28(A3)11-1.
5. Yuasa, S. et al. *Antiplatelet and antithrombotic effects of MS-180, novel GPIIb/IIIa antagonist*. Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-37.
6. *Mitsui Toatsu's antiplatelet agent slated to enter clinical testing*. Prous Science Daily Essentials 1997, Oct 6.

*Identified compound **250099** (see **249708**) Drug Data Rep 1997, 019(07): 0625.

UK-147535***210567**

3-[3-[2-(4-Chlorophenylsulfonamido)ethyl]-5-(4-fluorobenzyl)phenyl]propionic acid



C₂₄ H₂₃ Cl F N O₄ S; Mol wt: 475.9657

ACTION – Potent TxA₂ receptor antagonist (pA₂ = 10.6 for inhibition of U-46619-induced rat aorta contractions). Compound at doses of 0.1 and 1 mg/kg p.o. completely prevented *ex vivo* U-46619-induced platelet aggregation in dogs for > 12 and 48 h, respectively.

SOURCE – Pfizer.

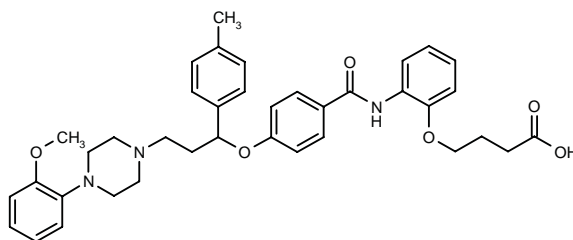
REFERENCES

1. Dickinson, R.P. et al. (Pfizer Ltd.;Pfizer Inc.) *Benzenealkanoic acids for cardiovascular diseases*. EP 662950, JP 96502046, US 5618941, WO 9406761.
2. Dack, K.N. et al. *Thromboxane modulating agents. 4. Design and synthesis of 3-(2-[(4-chlorophenyl)sulfonyl]amino)ethyl) benzenepropanoic acid derivatives as potent thromboxane receptor antagonists*. Bioorg Med Chem Lett 1998, 8(16): 2061.

*Identified compound **210567** (see **209346**) Drug Data Report 1994, 016(08): 0735.

RENAL-UROLOGIC DRUGS**BENIGN PROSTATIC HYPERPLASIA THERAPY****270078**

4-[2-[4-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(4-methylphenyl)propoxy]benzamido]phenoxy]butanoic acid

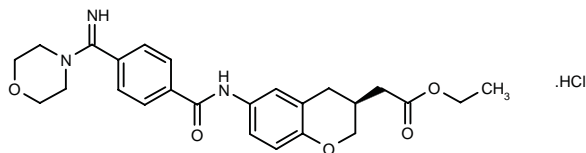


C₃₈ H₄₃ N₃ O₆; Mol wt: 637.7727

ACTION – Dual α₁-adrenoceptor antagonist and steroid 5α-reductase inhibitor, a benzanilide derivative proven to inhibit phenylephrine-induced contractions in rabbit prostate with a pA₂ of 7.8 and rat prostate 5α-reductase with an IC₅₀ of 0.067 μM. Potentially useful for ameliorating urethral obstruction caused by benign prostatic hyperplasia (BPH).

MS-180¹⁻⁶**248804**

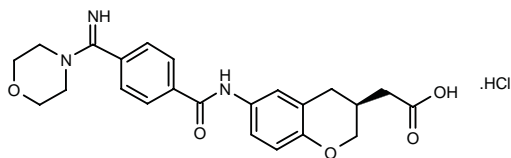
(–)-2-[6-[4-(4-Morpholinylcarbonimidoyl)benzamido]-3,4-dihydro-2H-1-benzopyran-3(S)-yl]acetic acid ethyl ester hydrochloride



C₂₅ H₂₉ N₃ O₅ . HCl; Mol wt: 487.981

Pale yellow solid, m.p. 242-4 °C, $[\alpha]_D^{20}$ –14.5° (c 1.0, MeOH).

ACTION – Orally active antiplatelet agent, a prodrug of **MS-28168**, a potent fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 0.12 nM) and platelet aggregation inhibitor (IC₅₀ = 44 nM against ADP-induced human platelet aggregation). After oral administration, compound dose-dependently inhibited *ex vivo* ADP-induced platelet aggregation in dogs at doses of 1-10 mg/kg (60, 85 and 100% inhibition, respectively, at 1, 3 and 10 mg/kg), and it inhibited thrombus formation in a guinea pig arteriovenous shunt model, being 200 and 50 times more potent than ticlopidine and aspirin, respectively. Selected as a candidate for clinical evaluation in the treatment of thrombosis.



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SOURCE – Mitsui Chemicals.

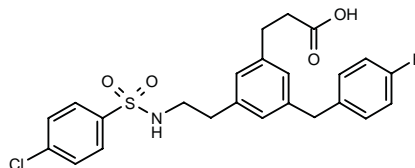
REFERENCES

1. Yamashita, H. et al. (Mitsui Chemicals, Inc.) *Amidine derivs. and platelet aggregation inhibitor containing the same*. EP 760364, JP 97124581, US 5719145.
2. Kawazura, H. et al. *Antithrombotic effect of MS-180, an orally active GPIIb/IIIa antagonist, on arterial thrombosis model in guinea-pigs*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-173.
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5. Yuasa, S. et al. *Antiplatelet and antithrombotic effects of MS-180, novel GPIIb/IIIa antagonist*. Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-37.
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UK-147535***210567**

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C₂₄ H₂₃ Cl F N O₄ S; Mol wt: 475.9657

ACTION – Potent TxA₂ receptor antagonist (pA₂ = 10.6 for inhibition of U-46619-induced rat aorta contractions). Compound at doses of 0.1 and 1 mg/kg p.o. completely prevented *ex vivo* U-46619-induced platelet aggregation in dogs for > 12 and 48 h, respectively.

SOURCE – Pfizer.

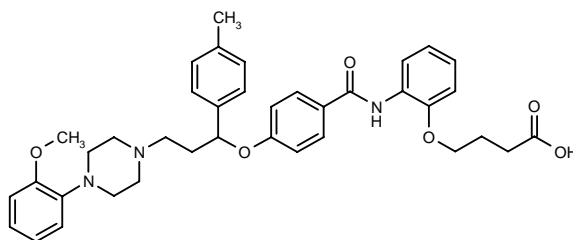
REFERENCES

1. Dickinson, R.P. et al. (Pfizer Ltd.;Pfizer Inc.) *Benzenealkanoic acids for cardiovascular diseases*. EP 662950, JP 96502046, US 5618941, WO 9406761.
2. Dack, K.N. et al. *Thromboxane modulating agents. 4. Design and synthesis of 3-(2-[(4-chlorophenyl)sulfonyl]amino)ethyl benzenepranoic acid derivatives as potent thromboxane receptor antagonists*. Bioorg Med Chem Lett 1998, 8(16): 2061.

*Identified compound **210567** (see **209346**) Drug Data Report 1994, 016(08): 0735.

RENAL-UROLOGIC DRUGS**BENIGN PROSTATIC HYPERPLASIA THERAPY****270078**

4-[2-[4-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(4-methylphenyl)propoxy]benzamido]phenoxy]butanoic acid



C₃₈ H₄₃ N₃ O₆; Mol wt: 637.7727

ACTION – Dual α₁-adrenoceptor antagonist and steroid 5α-reductase inhibitor, a benzaniide derivative proven to inhibit phenylephrine-induced contractions in rabbit prostate with a pA₂ of 7.8 and rat prostate 5α-reductase with an IC₅₀ of 0.067 μM. Potentially useful for ameliorating urethral obstruction caused by benign prostatic hyperplasia (BPH).

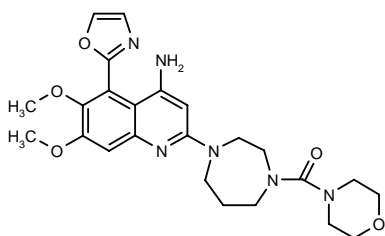
SOURCE – Zeria.

REFERENCES

1. Yoshida, K. et al. *Synthesis of benzanilide derivatives as dual acting agents with α_1 -adrenoceptor antagonistic action and steroid 5- α reductase inhibitory activity.* Bioorg Med Chem Lett 1998, 8(21): 2967.

270124

6,7-Dimethoxy-2-[4-(morpholin-4-ylcarbonyl)perhydro-1,4-diazepin-1-yl]-5-(oxazol-2-yl)quinolin-4-amine



C24 H30 N6 O5; Mol wt: 482.538

ACTION – Agent for the treatment of benign prostatic hyperplasia reported to be devoid of undesirable cardiovascular effects due to its selectivity for prostatic α_1 -adrenoceptors, shown to inhibit the contractile responses of human prostate elicited by (–)-norepinephrine with a pA_2 value of 9.2. A representative compound from a series of quinoline and quinazoline derivatives.

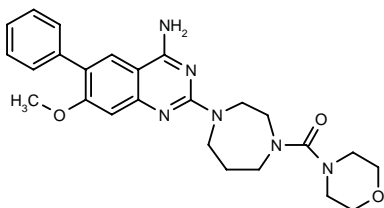
SOURCE – Pfizer.

REFERENCES

1. Fox, D.N.A. (Pfizer Ltd.;Pfizer Inc.) *Quinoline and quinazoline cpds. useful in therapy, particularly in the treatment of benign prostatic hyperplasia.* WO 9830560.

270188

7-Methoxy-2-[4-(morpholin-4-ylcarbonyl)perhydro-1,4-diazepin-1-yl]-6-phenylquinazolin-4-amine



C25 H30 N6 O3; Mol wt: 462.551

ACTION – Agent for the treatment of benign prostatic hyperplasia reported to be devoid of undesirable cardiovascular effects due to its selective prostatic α_1 -adrenoceptor-antagonist activity. *In vitro*, compound was tested for its ability to inhibit the contractile response of human prostate elicited by (–)-norepinephrine, giving a pA_2 value of 8.7. A representative compound from a series of quinoline and quinazoline derivatives.

SOURCE – Pfizer.

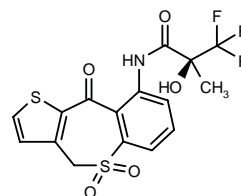
REFERENCES

1. Collis, A.J. and Fox, D.N.A. (Pfizer Ltd.;Pfizer Inc.) *Quinoline and quinazoline cpds. useful in therapy.* EP 875506, JP 98316664.

TREATMENT OF URINARY INCONTINENCE

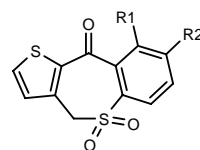
270488

3,3,3-Trifluoro-2-(S)-hydroxy-2-methyl-N-(10-oxo-4,10-dihydrothieno[3,2-c][1]benzothiepin-9-yl)propanamide 5,5-dioxide



C16 H12 F3 N O5 S2; Mol wt: 419.3988

ACTION – Agent for the treatment of urinary incontinence and pollakiuria whose activity was demonstrated by inhibition of KCl-induced contractions of guinea pig urinary bladder (IC_{50} = 2.6 and 10.5 μ M, respectively, at 15 and 50 mM KCl). *In vivo*, compound increased the interval between rat bladder contractions by 163% versus controls (100%) at 5 h postadministration when given at a dose of 0.1 mg/kg p.o., without significant effects on blood pressure or heart rate. Other tricyclic compounds include the following:



Compound	R1	R2	Formula
270489	NHCO-C(Me)(OH)CF ₃	H	C ₁₆ H ₁₂ F ₃ NO ₅ S ₂
270490	H	NHCO-C(Me)(OH)CF ₃	C ₁₆ H ₁₂ F ₃ NO ₅ S ₂

SOURCE – Kyowa Hakko.

REFERENCES

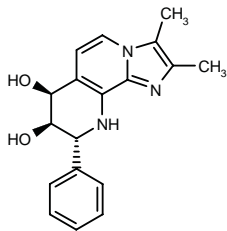
1. Yoshida, M. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tricyclic cpds.* WO 9846587.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

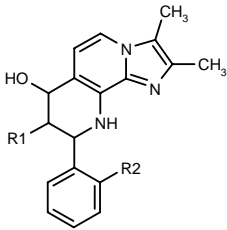
269661

(7*S*,8*R*,9*R*)-2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridine-7,8-diol



C18 H19 N3 O2; Mol wt: 309.3671

ACTION – Gastric acid antisecretory and antiulcer agent proven to completely inhibit acid secretion in rat perfused stomachs at a dose of 3 μmol/kg i.v. Other specifically claimed tetrahydropyrido compounds include the following:



Compound	R1	R2	Isomer	Formula
269662	H	H		C ₁₈ H ₁₉ N ₃ O
269663	H	Cl		C ₁₈ H ₁₈ ClN ₃ O
269664	OH	H		C ₁₈ H ₁₉ N ₃ O ₂
269665	OH	H	(<i>R,R,R</i>)	C ₁₈ H ₁₉ N ₃ O ₂

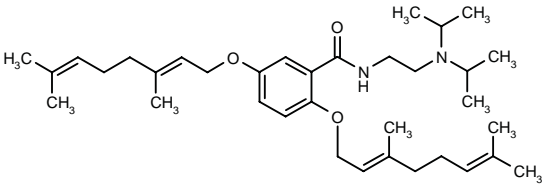
SOURCE – Byk Gulden.

REFERENCES

1. Simon, W.-A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Tetrahydropyrido cpds.* WO 9842707.

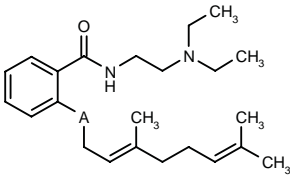
270203

N-[2-(Diisopropylamino)ethyl]-2,5-bis[3,7-dimethylocta-2(*E*),6-dienyloxy]benzamide

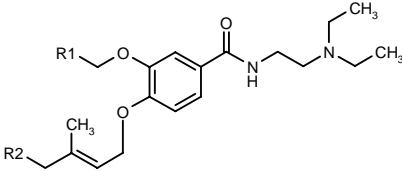


C35 H56 N2 O3; Mol wt: 552.8384

ACTION – Antiulcer agent with good antibacterial activity against *Helicobacter pylori* (MIC < 3.13 μg/ml) and gastric antisecretory activity (100.1% inhibition at 10 μM in isolated rabbit gastric fundic gland). It inhibited water immersion stress-induced ulcers in rats by 62% at a dose of 100 mg/kg p.o. No deaths were noted in mice after a single oral dose of 2000 mg/kg p.o. Within this series of alkylenediamine derivatives, the following are also included:



Compound	A	Formula
270206	O	C ₂₃ H ₃₆ N ₂ O ₂
270209	S	C ₂₃ H ₃₆ N ₂ OS



Compound	R1	R2	Formula
270208	CH=C(Me)2	H	C ₂₃ H ₃₆ N ₂ O ₃
270210	H	CH2CH=C(Me)2	C ₂₄ H ₃₈ N ₂ O ₃

SOURCE – Shiseido.

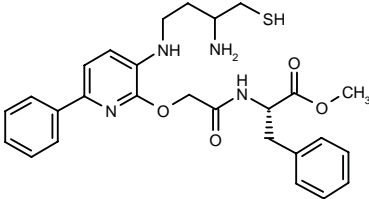
REFERENCES

1. Nishino, C. et al. (Shiseido Co. Ltd.) *Alkylenediamine deriv., anti-ulcer drug, and antibacterial drug.* EP 875501, JP 98279548.

INFLAMMATORY BOWEL DISEASE THERAPY

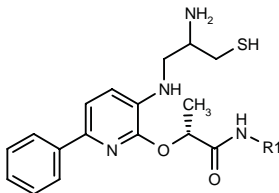
269936

N-[2-[3-(3-Amino-4-sulfanylbutamino)-6-phenylpyridin-2-yloxy]acetyl]-L-phenylalanine methyl ester

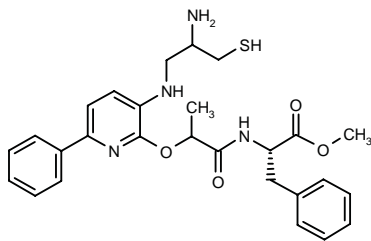


C27 H32 N4 O4 S; Mol wt: 508.6398

ACTION – Agent for the treatment of autoimmune and inflammatory disorders such as inflammatory bowel disease, asthma, allergic rhinitis, psoriasis, graft-versus-host disease, rheumatoid arthritis and multiple sclerosis that acts by inhibiting the proliferation of human T-lymphocytes ($IC_{50} < 0.05 \mu M$). Compound also inhibits prenyl transferases such as protein farnesyltransferase ($IC_{50} = 3.6 \text{ nM}$) and protein geranylgeranyltransferase I ($IC_{50} = 49 \text{ nM}$), and may also be useful for the treatment of cancer. Within this series of 3-aminopyridine derivatives, the following are also specifically claimed:



Compound	R1	Formula
269938	cyclohexyl-CH2	C ₂₄ H ₃₄ N ₄ O ₂ S
269939	2-Pyr-CH2	C ₂₃ H ₂₇ N ₅ O ₂ S
269940	3-NO ₂ -PhCH ₂	C ₂₄ H ₂₇ N ₅ O ₄ S
269941	2-Me-PhCH ₂	C ₂₅ H ₃₀ N ₄ O ₂ S
269942	2-MeO-PhCH ₂	C ₂₅ H ₃₀ N ₄ O ₃ S
269943	3-(MeSO ₂ NHCO)-PhCH ₂	C ₂₆ H ₃₁ N ₅ O ₅ S ₂
269944	3-(MeNHCO)-PhCH ₂	C ₂₆ H ₃₁ N ₅ O ₃ S
269945	2,6-(MeO)2-PhCH ₂	C ₂₆ H ₃₂ N ₄ O ₄ S
269946	2-(AcNH)-PhCH ₂	C ₂₆ H ₃₁ N ₅ O ₃ S
269947	2-Me-PhCH(Me)	C ₂₆ H ₃₂ N ₄ O ₂ S



269948: C27 H32 N4 O4 S

SOURCE – Ferring.

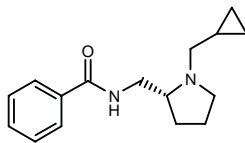
REFERENCES

1. Franklin, R.J. et al. (Ferring BV Group Holding) 3-Aminopyridine derivs. for treatment of inflammatory and malignant diseases. WO 9845266.

ANTIDIARRHEAL AGENTS

270883

N-[1-(Cyclopropylmethyl)pyrrolidin-2(*R*)-ylmethyl]-benzamide



C16 H22 N2 O; Mol wt: 258.3628

ACTION – Antidiarrheal agent found to be more potent than loperamide and acetorphan in murine models of secretory diarrhea induced by *Salmonella* lipopolysaccharide ($ED_{50} = 0.030 \text{ mg/kg p.o. vs. } 0.37 \text{ and } 34 \text{ mg/kg p.o.}$ for loperamide and acetorphan, respectively), the thermostable toxin of *Escherichia coli* ($ED_{50} = 0.015 \text{ mg/kg p.o. vs. } 3.92 \text{ mg/kg p.o.}$ for loperamide) and the A and B toxins of *Clostridium difficile* (95% inhibition at $0.05 \text{ mg/kg p.o. vs. } ED_{50} = 4.27 \text{ mg/kg p.o.}$ for loperamide). Compound was also found to potently inhibit intestinal secretion induced by cholera toxin in rats ($ED_{50} = 0.017 \text{ mg/kg p.o.}$). No mortality was observed following administration of up to 300 mg/kg p.o. to mice and no signs of toxicity were noted at doses below 100 mg/kg p.o. Compound was tested *in vitro* for affinity for σ - and dopamine receptors and was found to exhibit only weak affinity for σ -receptors ($IC_{50} = 784 \text{ nM}$) and no affinity for D_1 , D_2 or D_3 receptors ($IC_{50} > 10,000 \text{ nM}$).

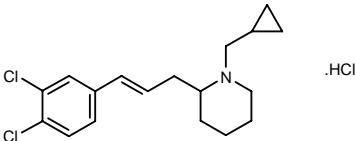
SOURCE – Jouveinal.

REFERENCES

1. Calvet, A. et al. (Jouveinal SA) (*R*)-*N*-(1-Cyclopropylmethylpyrrolidin-2-ylmethyl)benzamide and its use as an antidiarrhoeal. WO 9839295.

270915

(-)-1-(Cyclopropylmethyl)-2-[3-(3,4-dichlorophenyl)-2(*E*)-propenyl]piperidine hydrochloride



C18 H23 Cl2 N . HCl; Mol wt: 360.7536

ACTION – Broad-spectrum antidiarrheal agent, a σ -receptor ligand ($IC_{50} = 17.9 \text{ nM}$) found to be more potent than the racemate and than known antidiarrheal agents in murine models of secretory diarrhea induced by *Salmonella* lipopolysaccharide ($ED_{50} = 0.0056 \text{ mg/kg p.o. vs. } 0.038, 0.37 \text{ and } 34 \text{ mg/kg p.o.}$ for the racemate, loperamide and acetorphan, respectively), the thermostable toxin of *Escherichia coli* ($ED_{50} = 0.019 \text{ mg/kg p.o. vs. } 0.077 \text{ and } 3.92 \text{ mg/kg p.o.}$ for the racemate and loperamide, respectively) and the A and B toxins of *Clostridium difficile* ($ED_{50} < 0.001 \text{ mg/kg p.o. vs. } 0.058 \text{ and } 4.27 \text{ mg/kg p.o.}$ for the racemate and loperamide, respectively). Compound was also more potent than the racemate in inhibiting intestinal secretion induced by cholera toxin in rats ($ED_{50} = 0.038 \text{ mg/kg p.o. vs. } 1.9 \text{ mg/kg p.o.}$ for the racemate). No mortality was observed following administration of up to 300 mg/kg p.o. to mice and no signs of toxicity were noted at doses below 100 mg/kg p.o.

SOURCE – Jouveinal.

REFERENCES

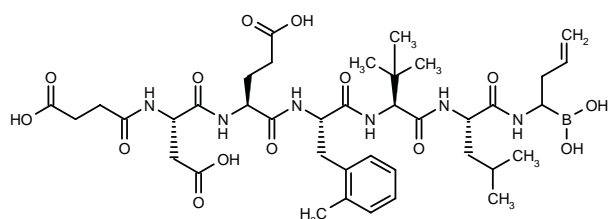
1. Calvet, A. et al. (Jouveinal SA) (-)-*E*-2-(3,4-Dichlorocinnamyl)-1-cyclopropylmethylpiperidine and its antidiarrhoeal use. WO 9839296.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

RO-32-6167

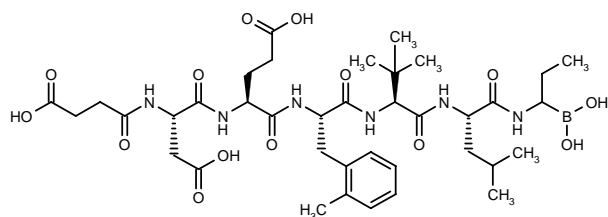
267685

N-(3-Carboxypropanoyl)-L-aspartyl-L-glutamyl-2-methyl-L-phenylalanyl-3-methyl-L-valyl-L-leucine *N*-(1-borono-3-butenyl)amide



C39 H59 B N6 O14; Mol wt: 846.7341

ACTION – Hepatitis C virus NS3-4A protease inhibitor with an IC_{50} value of 34 nM. Another chemically related compound is:



Ro-32-6168 [267752]: C38 H59 B N6 O14

SOURCE – Roche.

REFERENCES

1. Attwood, M.R. et al. (F. Hoffmann-La Roche AG) *Antiviral peptide derivs.* WO 9822496.
2. Attwood, M.R. et al. *The design and synthesis of potent inhibitors of hepatitis C virus NS3-4A proteinase.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.312.

ENDOCRINE DRUGS

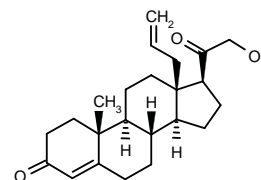
ADRENOCORTICAL DYSFUNCTION THERAPY

18-VDOC

270090

21-Hydroxy-18-vinylpregn-4-ene-3,20-dione

11-Deoxy-18-vinylcorticosterone



C23 H32 O3; Mol wt: 356.5028

Glassy solid.

ACTION – A potent, reversible and competitive inhibitor of bovine cytochrome P-450_{11β} (K_i = 0.3 μ M for 11 β -hydroxylation and 0.8 μ M for 18-hydroxylation), an analogue of deoxycorticosterone. Such compounds are potentially useful for decreasing aldosterone overproduction in pathological conditions.

SOURCE – CNRS.

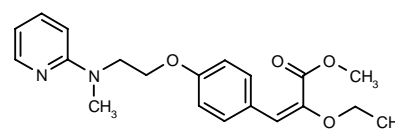
REFERENCES

1. Davioud, E. et al. *18-Vinyldeoxycorticosterone: A potent inhibitor of the bovine cytochrome P-450(11β).* Bioorg Med Chem 1998, 6(10): 1781.

ANTIDIABETIC DRUGS

269867

2-Ethoxy-3-[4-[2-[*N*-methyl-*N*-(2-pyridyl)amino]ethoxy]-phenyl]-2-propenoic acid methyl ester



C20 H24 N2 O4; Mol wt: 356.4196

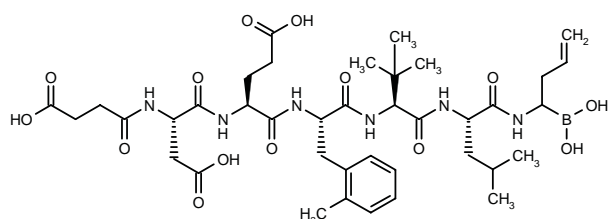
ACTION – Hypoglycemic and hypocholesterolemic agent whose blood glucose-lowering activity was demonstrated

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

RO-32-6167

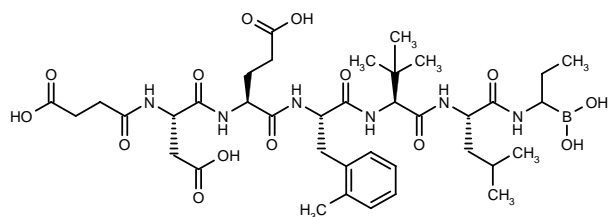
267685

N-(3-Carboxypropanoyl)-L-aspartyl-L-glutamyl-2-methyl-L-phenylalanyl-3-methyl-L-valyl-L-leucine *N*-(1-borono-3-butenyl)amide



C39 H59 B N6 O14; Mol wt: 846.7341

ACTION – Hepatitis C virus NS3-4A protease inhibitor with an IC_{50} value of 34 nM. Another chemically related compound is:



Ro-32-6168 [267752]: C38 H59 B N6 O14

SOURCE – Roche.

REFERENCES

1. Attwood, M.R. et al. (F. Hoffmann-La Roche AG) *Antiviral peptide derivs.* WO 9822496.
2. Attwood, M.R. et al. *The design and synthesis of potent inhibitors of hepatitis C virus NS3-4A proteinase.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.312.

ENDOCRINE DRUGS

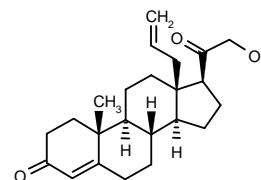
ADRENOCORTICAL DYSFUNCTION THERAPY

18-VDOC

270090

21-Hydroxy-18-vinylpregn-4-ene-3,20-dione

11-Deoxy-18-vinylcorticosterone



C23 H32 O3; Mol wt: 356.5028

Glassy solid.

ACTION – A potent, reversible and competitive inhibitor of bovine cytochrome P-450_{11β} (K_i = 0.3 μ M for 11 β -hydroxylation and 0.8 μ M for 18-hydroxylation), an analogue of deoxycorticosterone. Such compounds are potentially useful for decreasing aldosterone overproduction in pathological conditions.

SOURCE – CNRS.

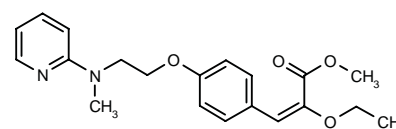
REFERENCES

1. Davioud, E. et al. *18-Vinyldeoxycorticosterone: A potent inhibitor of the bovine cytochrome P-450(11β).* Bioorg Med Chem 1998, 6(10): 1781.

ANTIDIABETIC DRUGS

269867

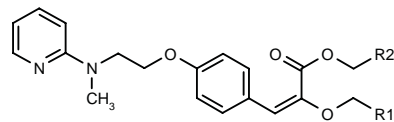
2-Ethoxy-3-[4-[2-[*N*-methyl-*N*-(2-pyridyl)amino]ethoxy]-phenyl]-2-propenoic acid methyl ester



C20 H24 N2 O4; Mol wt: 356.4196

ACTION – Hypoglycemic and hypocholesterolemic agent whose blood glucose-lowering activity was demonstrated

in *ob/ob* mice (56% decrease at a dose of 10 µmol/kg diet). Other specifically claimed heterocyclic compounds include the following:



Compound	R1=R2	Isomer	Formula
269868	H		C ₁₉ H ₂₂ N ₂ O ₄
269869	Me	Z	C ₂₁ H ₂₆ N ₂ O ₄
269870	Me	E	C ₂₁ H ₂₆ N ₂ O ₄

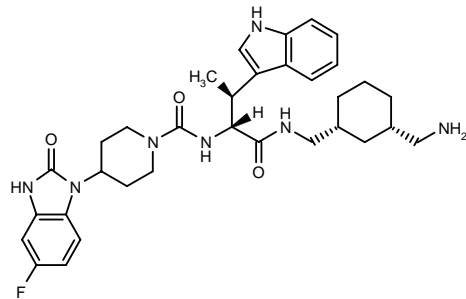
SOURCE – SmithKline Beecham.

REFERENCES

1. Haigh, D. and Sime, J.T. (SmithKline Beecham plc) *Heterocyclic cpds. as pharmaceutical*. US 5827865.

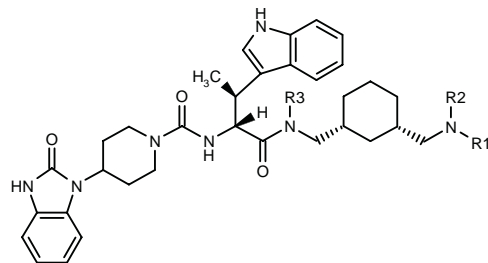
269871

*N*¹-[3(*S*)-(Aminomethyl)-1(*R*)-cyclohexylmethyl]-*N*²-[4-(5-fluoro-2-oxobenzimidazolin-1-yl)piperidin-1-ylcarbonyl]-3(*S*)-methyl-D-tryptophanamide



C33 H42 F N7 O3; Mol wt: 603.7388

ACTION – Somatostatin receptor agonist with selectivity for the sst2 receptor subtype, potentially useful for the treatment or prevention of diabetes, cancer, acromegaly, restenosis, depression, irritable bowel syndrome, pain and diabetic retinopathy. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	R3	Formula
269872	Me	Me	H	C ₃₅ H ₄₇ N ₇ O ₃
269873	H	H	H	C ₃₃ H ₄₃ N ₇ O ₃
269874	H	cyclopropyl	H	C ₃₆ H ₄₇ N ₇ O ₃
269875	H	H	Me	C ₃₄ H ₄₅ N ₇ O ₃
269876	H	H	cyclopropyl	C ₃₆ H ₄₇ N ₇ O ₃

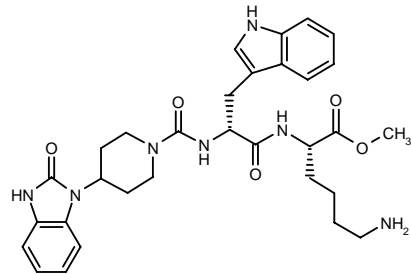
SOURCE – Merck & Co.

REFERENCES

1. Yang, L. et al. (Merck & Co., Inc.) *Somatostatin agonists*. WO 9844921.

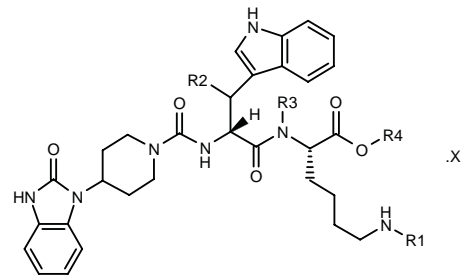
269914

N-[4-(2-Oxobenzimidazolin-1-yl)piperidin-1-ylcarbonyl]-D-tryptophyl-L-lysine methyl ester

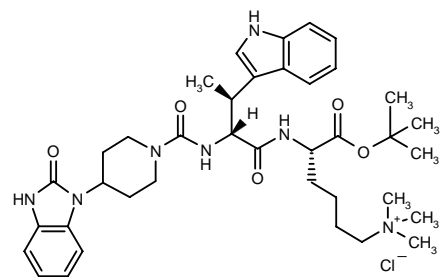


C31 H39 N7 O5; Mol wt: 589.6931

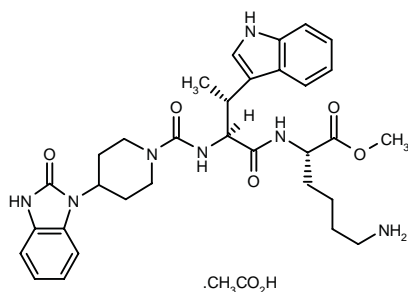
ACTION – Orally active somatostatin receptor agonist for the treatment of diabetes, cancer, acromegaly, restenosis, depression, irritable bowel syndrome, pain and diabetic retinopathy. It showed selectivity for the sst2 subtype, and was also found to be capable of inhibiting mediators of neurogenic inflammation such as substance P. Within this series of specifically claimed compounds, the following are also included:



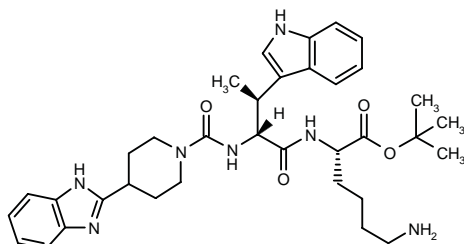
Compound	R1	R2	R3	R4	X	Formula
269916	H	Me	Me	Me		C ₃₃ H ₄₃ N ₇ O ₅
269917	C(=NH)NH2	(S)-Me	H	t-Bu		C ₃₆ H ₄₉ N ₉ O ₅
269918	H	(S)-Me	H	t-Bu		C ₃₅ H ₄₇ N ₇ O ₅
269921	H	(S)-Me	H	Me	acetate	C ₃₂ H ₄₁ N ₇ O ₅ .C ₂ H ₄ O ₂



269919: C38 H54 Cl N7 O5



269920: C₃₂ H₄₁ N₇ O₅ . C₂ H₄ O₂



269923: C₃₅ H₄₇ N₇ O₄

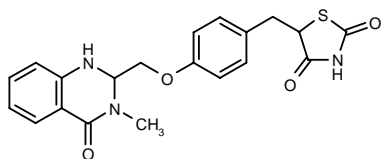
SOURCE – Merck & Co.

REFERENCES

1. Yang, L. et al. (Merck & Co., Inc.) *Somatostatin agonists*. WO 9844922.

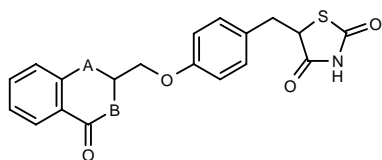
269959

5-[4-(3-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione



C₂₀ H₁₉ N₃ O₄ S; Mol wt: 397.4531

ACTION – Antidiabetic agent proven to lower blood glucose and triglyceride levels in *db/db* mice when administered at 3 mg/kg/day p.o. x 6 days (55 and 35% reduction, respectively); compound is also reported to lower cholesterol levels in these animals. A representative compound from a series of thiazolidinedione and oxazolidinedione derivatives, wherein the following are also included:



Compound	A	B	Formula
269960	N(Me)	N(Me)	C ₂₁ H ₂₁ N ₃ O ₄ S
269961	O	N(Me)	C ₂₀ H ₁₈ N ₂ O ₅ S
269962	O	NH	C ₁₉ H ₁₆ N ₂ O ₅ S

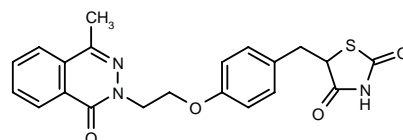
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

REFERENCES

1. Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Substd. thiazolidinedione and oxazolidinedione having antidiabetic, hyperlipidemia and antihypertensive properties*. WO 9845291.

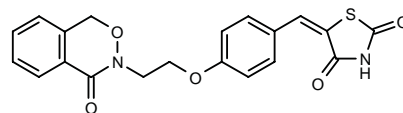
269963

5-[4-[2-(4-Methyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione



C₂₁ H₁₉ N₃ O₄ S; Mol wt: 409.4641

ACTION – Antidiabetic agent proven to lower blood glucose and triglyceride levels in *db/db* mice when administered at 10 mg/kg/day p.o. x 6 days (61 and 40% reduction, respectively); compound is also reported to lower cholesterol levels in these animals. Another compound from this series of thiazolidinedione and oxazolidinedione derivatives is:



269964: C₂₀ H₁₆ N₂ O₅ S

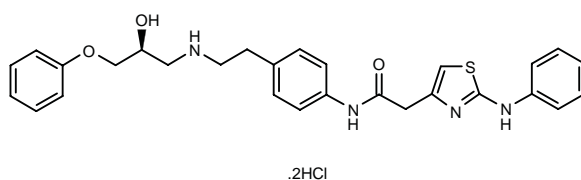
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

REFERENCES

1. Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Thiazolidinedione and oxazolidinedione derivs. having antidiabetic, hypolipidaemic and antihypertensive properties*. WO 9845292.

270470

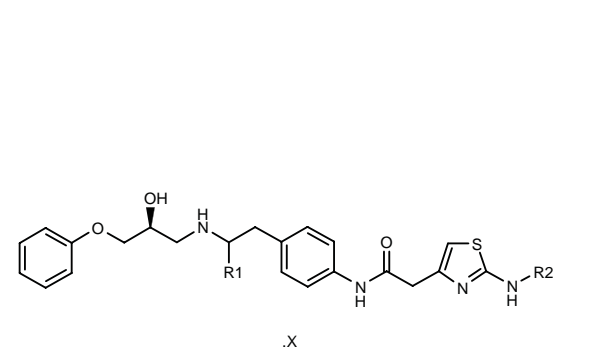
N-[4-[2-[2-(S)-Hydroxy-3-phenoxypropylamino]-ethyl]phenyl]-2-[2-(phenylamino)thiazol-4-yl]acetamide dihydrochloride



C₂₈ H₃₀ N₄ O₃ S . 2HCl; Mol wt: 575.5578

ACTION – Antidiabetic agent that acts by enhancing both insulin sensitivity and secretion. Compound reduced blood glucose levels in diabetic mice by 56% at 10 mg/kg/day p.o. x 4 days. In addition, it was shown to increase insulin secretion by 3-fold when given to glucose-

treated rats at 10 mg/kg p.o. Within this series of amide derivatives, the following are also included:



Compound	R1	R2	X	Formula
270471	H	CH2Ph		C ₂₉ H ₃₂ N ₄ O ₃ S
270472	H	3-F-Ph	2HCl	C ₂₈ H ₂₉ FN ₄ O ₃ S.2HCl
270473	Me	Ph	2HCl	C ₂₉ H ₃₂ N ₄ O ₃ S.2HCl

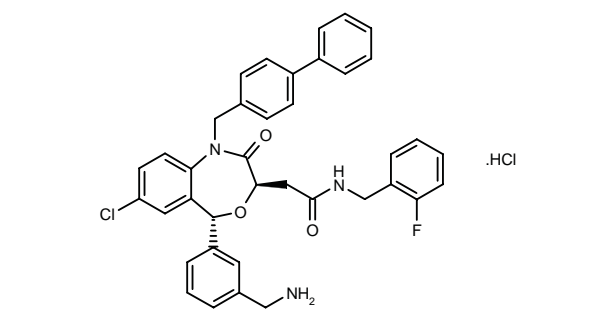
SOURCE – Yamanouchi.

REFERENCES

1. Maruyama, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel amide derivs. and medicinal compsns. thereof.* WO 9832742.

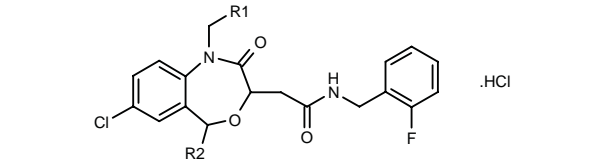
270675

trans-2-[5-[3-(Aminomethyl)phenyl]-1-(biphenyl-4-ylmethyl)-7-chloro-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-*N*-(2-fluorobenzyl)acetamide hydrochloride



C38 H33 Cl F N3 O3 . HCl; Mol wt: 670.6086

ACTION – Nonpeptide somatostatin receptor agonist with selectivity for the sst5 subtype relative to other subtypes, as demonstrated in binding assays (IC₅₀ = 0.0007 μM; IC₅₀ sst1, sst2, sst3 and sst4 = 1, 0.1, 0.003 and 0.3 μM, respectively), and in functional assays of inhibition of forskolin-stimulated cAMP accumulation in CHO cells stably transfected with human somatostatin receptor subtypes (EC₅₀ = 0.7 nM; EC₅₀ sst2, sst3 and sst4 = 300, 2 and 200 nM, respectively). It was also shown to inhibit growth hormone (GH) release in the rat pituitary cell assay (IC₅₀ = 8 nM). *In vivo*, it significantly inhibited GH secretion in rats at 3 mg/kg i.p. and it was found to inhibit glucose-stimulated insulin secretion in rats with an ID₅₀ value of about 0.03 mg/kg i.v. Claimed for the treatment or prevention of diabetes, diabetic complications, obesity and chronic diarrhea. Other compounds within this series of 4,1-benzoxazepines include the following:



Compound	R1	R2	Isomer	Formula
270676	t-Bu	3-(NH2CH2)-Ph	3S,5S	C ₃₀ H ₃₃ ClFN ₃ O ₃ .HCl
270677	4-Ph-Ph	4-(NH2CH2)-Ph	trans	C ₃₈ H ₃₃ ClFN ₃ O ₃ .HCl
270678	4-MeO-Ph	5-(NH2CH2)-2-thienyl	trans	C ₃₁ H ₂₉ ClFN ₃ O ₄ S.HCl
270680	4-Ph-Ph	3-[NH2-C(Me)2]-Ph	trans	C ₄₀ H ₃₇ ClFN ₃ O ₃ .HCl
270682	4-OH-Ph	3-(NH2CH2)-Ph	trans	C ₃₂ H ₂₉ ClFN ₃ O ₄ .HCl

SOURCE – Takeda.

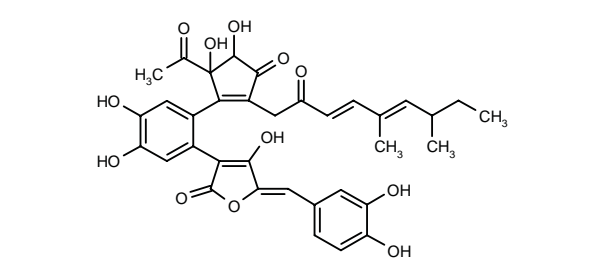
REFERENCES

1. Mabuchi, H. et al. (Takeda Chemical Industries, Ltd.) *4,1-Benzoxazepines, their analogues, and their use as somatostatin agonists.* WO 9847882.

KODAISTATIN C

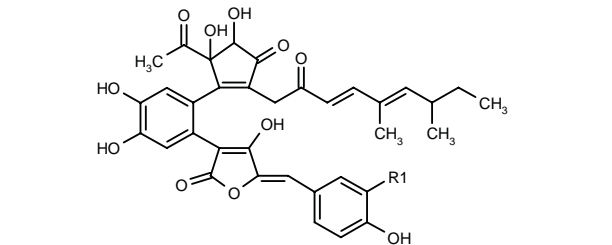
270749

(-)-3-[2-[5-Acetyl-2-(5,7-dimethyl-2-oxo-3,5-nonadienyl)-4,5-dihydroxy-3-oxo-1-cyclopenten-1-yl]-4,5-dihydroxyphenyl]-5-(3,4-dihydroxybenzylidene)-4-hydroxy-2(5*H*)-furanone



C35 H34 O12; Mol wt: 646.6416

ACTION – Antidiabetic agent isolated from a culture of the microorganism *Aspergillus terreus* Thom. HIL-051652 (DSM 11247), that acts by inhibiting glucose-6-phosphate translocase (IC₅₀ = 0.09 μg/ml against enzyme from rat liver microsomes), the component of hepatic glucose-6-phosphatase that facilitates transport into the endoplasmic reticulum lumen. Other compounds isolated from the same source are:



Compound	R1	Isomer	Formula
Kodaistatin A [270750]	H	(-)	C ₃₅ H ₃₄ O ₁₁
Kodaistatin B [270751]	H		C ₃₅ H ₃₄ O ₁₁
Kodaistatin D [270752]	OH		C ₃₅ H ₃₄ O ₁₂

SOURCE – Hoechst Marion Roussel.

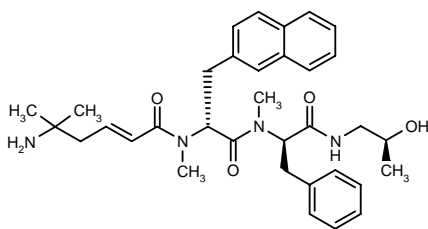
REFERENCES

1. Ramakrishna, N.V.S. et al. (Hoechst Marion Roussel Deutschland GmbH) *Kodaistatins A, B, C and D, a process for their production and their use.* WO 9847888.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

268333

N-[5-Amino-5-methyl-2(*E*)-hexenoyl]-*N*-methyl-3-(2-naphthyl)-*D*-alanyl-*N*-methyl-*D*-phenylalanine *N*-[2(*S*)-hydroxypropyl]amide



C34 H44 N4 O4; Mol wt: 572.7456

ACTION – Orally active growth hormone (GH) secretagogue, as demonstrated in cultured rat pituitary cells (EC_{50} = 8.9 nM) and *in vivo* in pigs (ED_{50} = 31 nmol/kg i.v.). Although it is about 8 times less potent than the original lead hexapeptide GHRP-6, it is orally bioavailable.

SOURCE – Novo Nordisk.

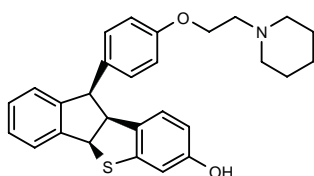
REFERENCES

1. Eriksen, E.F. and Kappelgaard, A.-M. (Novo Nordisk A/S) *Growth hormone component and bone anti-resorptive agent in cyclic (coherence) treatment of osteoporosis.* WO 9746252.
2. Hansen, T.K. et al. (Novo Nordisk A/S) *Cpds. with growth hormone releasing properties.* WO 9723508.
3. Hansen, T.K. et al. *Novel orally active growth hormone secretagogues.* J Med Chem 1998, 41(19): 3705.

TREATMENT OF GYNECOLOGICAL DISORDERS

270189

(4*R*,9*bS*,10*R*)-10-[2-(1-Piperidinyloxy)-9*b*,10-dihydro-4*bH*-benz[*b*]indeno[2,1-*d*]thiophen-7-ol



C28 H29 N O2 S; Mol wt: 443.6081

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancers such as breast or uterine cancer. In ovariectomized rats, compound significantly decreased serum cholesterol levels at 1 and 10 mg/kg/day p.o. x 4 days (35.7 and 65.0%, respectively), with little stimulatory effect on the uterus or on eosinophil infiltration into the uterus, contrary to the effects observed with 17 α -ethinylestradiol (0.1 mg/kg/day p.o. x 4 days). In addition, it inhibited the proliferation of breast adenocarcinoma MCF-7 cells with an IC_{50} value of 100 nM.

SOURCE – Lilly.

REFERENCES

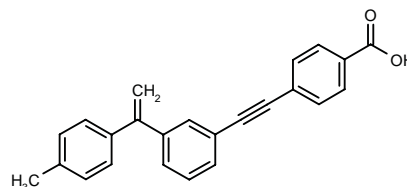
1. Bell, M.G. et al. (Eli Lilly and Company) *Dihydrobenzo[*b*]indeno[2,1-*d*]thiophene cpds., intermediates, processes, compsns. and methods.* US 5834488.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

270788

4-[3-[1-(4-Methylphenyl)vinyl]phenylethynyl]benzoic acid



C24 H18 O2; Mol wt: 338.4042

ACTION – Compound with retinoid-like activity tested *in vitro* for its binding affinity for the retinoic acid receptor subtypes $RAR\alpha$, $RAR\beta$ and $RAR\gamma$ (K_i > 1000, 224 and >1000 nM, respectively). It acts as a retinoid antagonist or inverse agonist, as demonstrated by its lack of activity in a transactivation assay. Potentially useful for the treatment of skin-related diseases including keratoses, acne, psoriasis, eczema, atopic dermatitis and hyperproliferative disorders, including cancerous and precancerous conditions. A representative compound from a series of trisubstituted phenyl derivatives acting as agonists, antagonists or inverse agonists at retinoid receptors, wherein the following are also included:

SOURCE – Hoechst Marion Roussel.

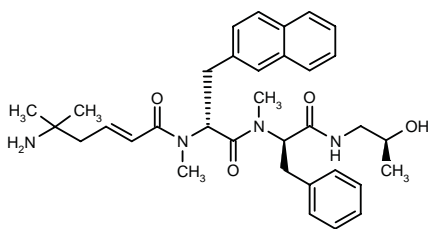
REFERENCES

1. Ramakrishna, N.V.S. et al. (Hoechst Marion Roussel Deutschland GmbH) *Kodaistatins A, B, C and D, a process for their production and their use.* WO 9847888.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

268333

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SOURCE – Novo Nordisk.

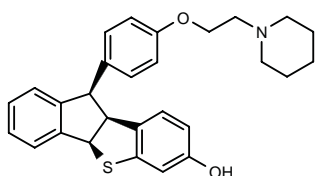
REFERENCES

1. Eriksen, E.F. and Kappelgaard, A.-M. (Novo Nordisk A/S) *Growth hormone component and bone anti-resorptive agent in cyclic (coherence) treatment of osteoporosis.* WO 9746252.
2. Hansen, T.K. et al. (Novo Nordisk A/S) *Cpds. with growth hormone releasing properties.* WO 9723508.
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SOURCE – Lilly.

REFERENCES

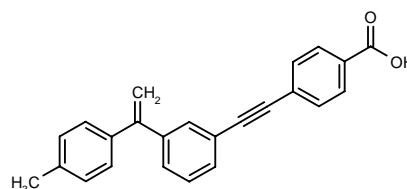
1. Bell, M.G. et al. (Eli Lilly and Company) *Dihydrobenzo[*b*]indeno[2,1-*d'*]thiophene cpds., intermediates, processes, compsns. and methods.* US 5834488.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

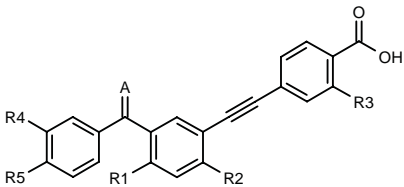
270788

4-[3-[1-(4-Methylphenyl)vinyl]phenylethynyl]benzoic acid



C24 H18 O2; Mol wt: 338.4042

ACTION – Compound with retinoid-like activity tested *in vitro* for its binding affinity for the retinoic acid receptor subtypes RAR α , RAR β and RAR γ (K_i > 1000, 224 and >1000 nM, respectively). It acts as a retinoid antagonist or inverse agonist, as demonstrated by its lack of activity in a transactivation assay. Potentially useful for the treatment of skin-related diseases including keratoses, acne, psoriasis, eczema, atopic dermatitis and hyperproliferative disorders, including cancerous and precancerous conditions. A representative compound from a series of trisubstituted phenyl derivatives acting as agonists, antagonists or inverse agonists at retinoid receptors, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
270789	OH	H	H	H	Me	C ₂₃ H ₁₆ O ₄
270790	OH	H	H	H	Me	C ₂₄ H ₁₈ O ₃
270791	OCH ₂ OMe	H	H	H	Me	C ₂₆ H ₂₂ O ₄
270792	OMe	H	H	H	Me	C ₂₅ H ₂₀ O ₃
270793	OCH ₂ OMe	H	H	H	Me	C ₂₅ H ₂₀ O ₅
270794	OMe	H	H	H	Me	C ₂₄ H ₁₈ O ₄
270795	OH	Me	F	H	Me	C ₂₄ H ₁₇ FO ₄
270796	i-PrO	H	H	H	Me	C ₂₇ H ₂₄ O ₃
270797	i-PrO	H	F	H	Me	C ₂₇ H ₂₃ FO ₃
270798	i-PrO	H	H	Me	H	C ₂₇ H ₂₄ O ₃

SOURCE – Allergan.

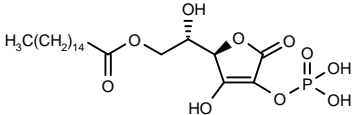
REFERENCES

1. Song, T.K. et al. (Allergan, Inc.) *Trisubst. phenyl derivs. having retinoid agonist, antagonist or inverse agonist type biological activity.* WO 9847854.

MISCELLANEOUS
DERMATOLOGIC DRUGS

270173

6-O-Hexadecanoyl-2-O-phosphono-L-ascorbic acid



C22 H39 O10 P; Mol wt: 494.5141

ACTION – Novel ascorbic acid derivative with the activity of vitamin C and improved stability and liposolubility, as well as increased cellular uptake, as compared to ascorbic acid or other previously reported derivatives. Potentially useful for the treatment of dermatological disorders, arrhythmias, cerebral infarction and for inhibiting cancer metastasis.

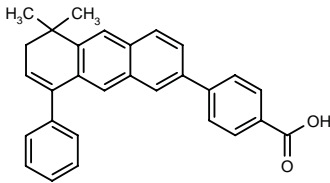
SOURCE – Showa Denko.

REFERENCES

1. Suzuki, M. et al. (Showa Denko KK) *Ascorbic acid deriv. and vitamin C preparation containing the same.* EP 875514.

270841

4-(5,5-Dimethyl-8-phenyl-5,6-dihydro-2-anthracenyl)-benzoic acid



C29 H24 O2; Mol wt: 404.5066

ACTION – Retinoid-like compound with potential in the treatment of chronic skin inflammatory diseases such as psoriasis and atopic dermatitis, rheumatic diseases such as rheumatoid arthritis, nonmalignant proliferative skin conditions and malignant tumors, and particularly for preventing postsurgical adhesion formation. *In vivo*, compound was found to dose-dependently prevent the formation of trauma-induced cecal adhesions in rats following oral administration of 3-25 mg/kg. In addition, it was found to be comparable to *all-trans*-retinoic acid when assessed for its effects on the differentiation and apoptosis of HL-60 cells.

SOURCE – Bristol-Myers Squibb.

REFERENCES

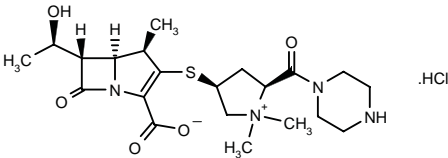
1. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Retinoid-like cpds.* WO 9849136.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

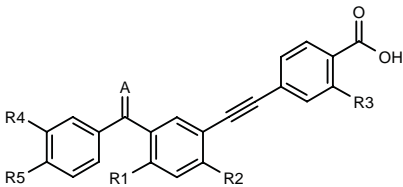
268613²

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1,1-dimethyl-2(*S*)-(piperazin-1-ylcarbonyl)pyrrolidinium-4(*S*)-ylsulfany]-1-carbapen-2-em-3-carboxylic acid inner salt hydrochloride



C21 H32 N4 O5 S . HCl; Mol wt: 489.0337

Colorless powder.



Compound	R1	R2	R3	R4	R5	Formula
270789	OH	H	H	H	Me	C ₂₃ H ₁₆ O ₄
270790	OH	H	H	H	Me	C ₂₄ H ₁₈ O ₃
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270792	OMe	H	H	H	Me	C ₂₅ H ₂₀ O ₃
270793	OCH ₂ OMe	H	H	H	Me	C ₂₅ H ₂₀ O ₅
270794	OMe	H	H	H	Me	C ₂₄ H ₁₈ O ₄
270795	OH	Me	F	H	Me	C ₂₄ H ₁₇ FO ₄
270796	i-PrO	H	H	H	Me	C ₂₇ H ₂₄ O ₃
270797	i-PrO	H	F	H	Me	C ₂₇ H ₂₃ FO ₃
270798	i-PrO	H	H	Me	H	C ₂₇ H ₂₄ O ₃

SOURCE – Allergan.

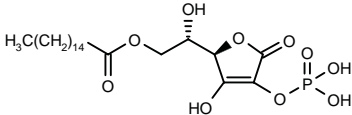
REFERENCES

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MISCELLANEOUS
DERMATOLOGIC DRUGS

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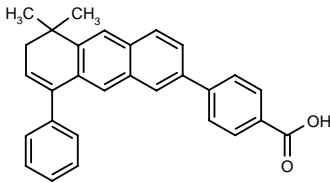
SOURCE – Showa Denko.

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270841

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SOURCE – Bristol-Myers Squibb.

REFERENCES

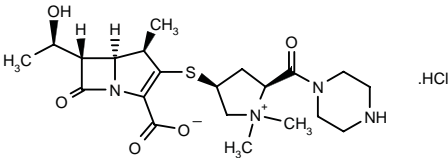
1. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Retinoid-like cpds.* WO 9849136.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

268613²

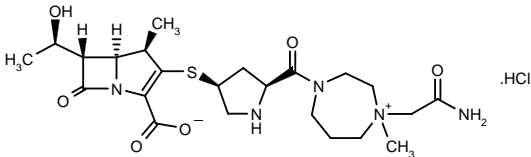
(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1,1-dimethyl-2(*S*)-(piperazin-1-ylcarbonyl)pyrrolidinium-4(*S*)-ylsulfany]-1-carbapen-2-em-3-carboxylic acid inner salt hydrochloride



C21 H32 N4 O5 S . HCl; Mol wt: 489.0337

Colorless powder.

ACTION – β -Methylcarbapenem antibiotic with potent and well-balanced activity against both Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC < 0.01-0.05 $\mu\text{g/ml}$), methicillin-resistant *S. aureus* (MIC = 6.2 $\mu\text{g/ml}$), *Escherichia coli* (MIC = 0.1-0.2 $\mu\text{g/ml}$), *Klebsiella pneumoniae* (MIC = 0.05 $\mu\text{g/ml}$) and *Pseudomonas aeruginosa* (MIC = 0.4 $\mu\text{g/ml}$). *In vivo*, compound showed good protection against murine infections induced by *S. aureus* Smith, *E. coli* 704 and *P. aeruginosa* 1008, giving ED₅₀ values of 0.36, 1.37 and 1.00 mg/kg s.c., respectively. It also displayed good urinary recovery (98% after 50 mg/kg s.c.) and low acute toxicity in mice. Within this series of 1 β -methylcarbapenems, the following is also included:



268614^{1,2}: C23 H35 N5 O6 S . HCl

SOURCE – Sankyo.

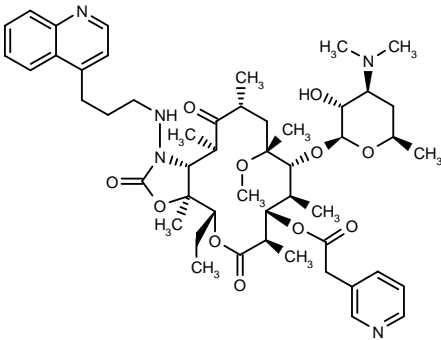
REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Carbapenem derivs. having antibiotic activity, their preparation and their use*. EP 443883, JP 92211083, US 5310735.

2. Ishikawa, K. et al. *Synthesis and structure-activity relationships of 1beta-methylcarbapenems with quaternary ammonium side chains*. J Antibiot 1998, 51(8): 757.

269844

11-Deoxy-3-*O*-des(hexopyranosyl)-6-*O*-methyl-3-*O*-[2-(3-pyridyl)acetyl]-11-[2-[3-(4-quinolinyl)propyl]hydrazino]-erythromycin A 11-*N*¹,12-*O*-cyclic carbamate



C50 H71 N5 O11; Mol wt: 918.1349

ACTION – Erythromycin A derivative active *in vitro* against erythromycin-sensitive and certain erythromycin-resistant bacteria including *Staphylococcus aureus* B1 (MIC = 0.1 $\mu\text{g/ml}$) and *Streptococcus pneumoniae* BM205 (MIC = 0.39 $\mu\text{g/ml}$).

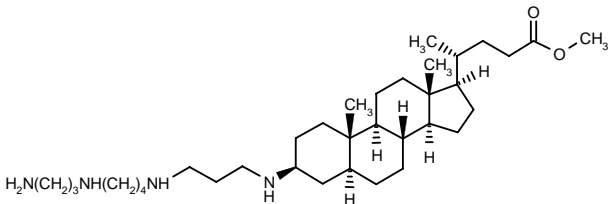
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs*. WO 9842720.

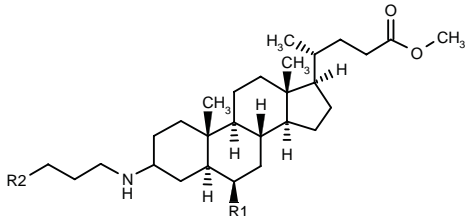
270127

3 β -(12-Amino-4,9-diazadodecylamino)-5 α -cholan-24-oic acid methyl ester



C35 H66 N4 O2; Mol wt: 574.9324

ACTION – Aminosterol antibiotic that acts as an Na⁺/H⁺ exchange (NHE) inhibitor and shows antimicrobial activity against various microorganisms such as *Staphylococcus aureus* (MIC = 1-2 $\mu\text{g/ml}$), *Escherichia coli* (MIC = 32 $\mu\text{g/ml}$), *Pseudomonas aeruginosa* (MIC = 64 $\mu\text{g/ml}$) and *Candida albicans* (MIC = 2 $\mu\text{g/ml}$). Compound also shows antiangiogenic and antitumor properties (IC₅₀ = 5.0 $\mu\text{g/ml}$ against melanoma cells in an MTT assay) and is reported to induce swelling of red blood cells, thus being additionally useful for the treatment of malaria and sickle cell anemia. Within this series of aminosterol ester derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
270128	OH	NH(CH2)4NH(CH2)3NH2	3 β	C ₃₅ H ₆₆ N ₄ O ₃
270129	OH	NH(CH2)4NH2	3 β	C ₃₂ H ₅₉ N ₃ O ₃
270130	H	NH(CH2)2NHCH2)3NH2	3 α	C ₃₅ H ₆₆ N ₄ O ₂
270133	OH	4-[NH2(CH2)3]-1-Piz	3 β	C ₃₅ H ₆₄ N ₄ O ₃

Certain compounds within the scope of the invention also inhibit HIV.

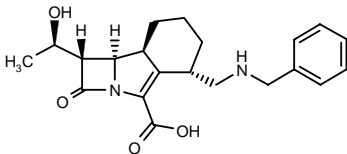
SOURCE – Magainin.

REFERENCES

1. Zasloff, M. et al. (Magainin Pharmaceuticals Inc.) *Aminosterol ester cpds*. WO 9827106.

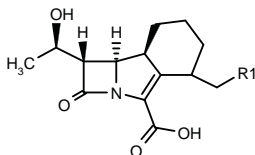
270309

(4*S*,8*S*,9*R*,10*S*)-4-(Benzylaminomethyl)-10-[1(*R*)-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid



C21 H26 N2 O4; Mol wt: 370.4464

ACTION – Antibacterial agent with potent and broad-spectrum activity against Gram-positive bacteria such as *Staphylococcus aureus* 209P (MIC = 0.01 µg/ml or less) and methicillin-resistant *S. aureus* 535 (MIC = 3.1 µg/ml); the reference compound sanfetrinem gave respective MICs of 0.02 and 12.5 µg/ml. Within this series of tricyclic β-lactam compounds, the following are also included:



Compound	R1	Isomer	Formula
270310	3(S)-pyrrolidinyl-S	R	C ₁₈ H ₂₆ N ₂ O ₄ S
270311	2-thiazolyl-NH	S	C ₁₇ H ₂₁ N ₃ O ₄ S

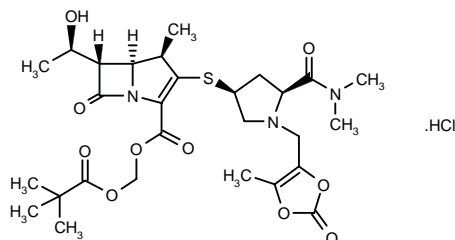
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Tricyclic heterocyclic cpds.* JP 98279581, WO 9834937.

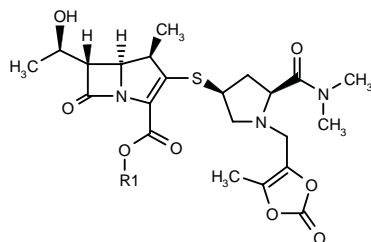
270399

(1*R*,5*S*,6*S*)-2-[5(*S*)-(*N,N*-Dimethylcarbamoyl)-1-(5-methyl-2-oxo-1,3-dioxol-4-ylmethyl)pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid pivaloyloxymethyl ester hydrochloride



C28 H39 N3 O10 S . HCl; Mol wt: 646.154

ACTION – Carbapenem antibiotic with good oral absorption and a broad spectrum of antibacterial activity. Other carbapenem compounds include the following:



Compound	R1	Formula
270400	4-NO ₂ -PhCH ₂	C ₂₉ H ₃₄ N ₄ O ₁₀ S
270401	Na	C ₂₂ H ₂₈ N ₃ NaO ₈ S
270402	t-BuCOOCH ₂	C ₂₈ H ₃₉ N ₃ O ₁₀ S

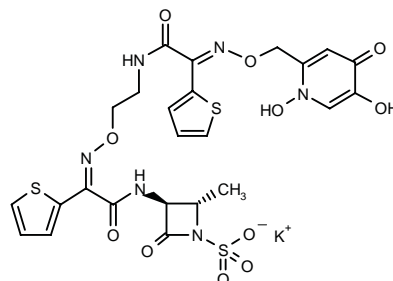
SOURCE – Kyoto Pharmaceutical.

REFERENCES

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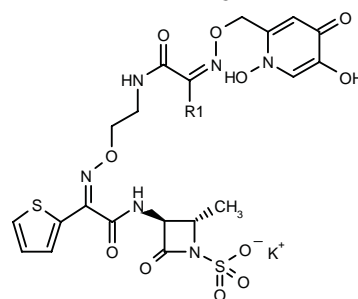
270770

(2*S*,3*S*)-3-[2(*E*)-[2-[2(*Z*)-(1,5-Dihydroxy-4-oxo-1,4-dihydropyridin-2-ylmethoxyimino)-2-(2-thienyl)-acetamido]ethoxyimino]-2-(2-thienyl)acetamido]-2-methyl-4-oxoazetidine-1-sulfonic acid potassium salt

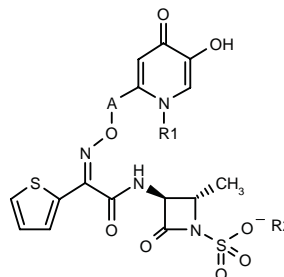


C24 H23 K N6 O11 S3; Mol wt: 706.7727

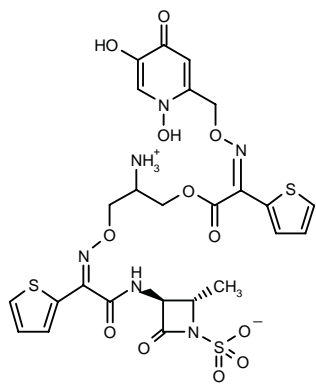
ACTION – Potent β-lactamase inhibitor, particularly active against class C β-lactamases (cephalosporinases), for use in combination with β-lactam antibiotics to increase their effectiveness against infections caused by β-lactamase-producing bacteria, particularly *Pseudomonas aeruginosa*. Compound exhibited an IC₅₀ value of 0.001 µM against cephalosporinase compared to a value of 0.13 µM for the reference compound aztreonam. It exhibited excellent synergy when given in combination with ceftazidime at a concentration of 10 µg/ml; for example, the MIC values against *Enterobacter cloacae* 40054 and *P. aeruginosa* 46220 DR-2-1 were < 0.25 and < 0.25 µg/ml, respectively, compared to > 32 and > 32 µg/ml, respectively, when ceftazidime was tested alone or in combination with aztreonam at 10 µg/ml. A representative compound from a series of 2-oxo-1-azetidinesulfonic acid derivatives, wherein the following are also included:



Compound	R1	Formula
270772	2-thienyl	C ₂₄ H ₂₃ KN ₆ O ₁₁ S ₃
270773	2-NH2-4-thiazolyl	C ₂₃ H ₂₃ KN ₆ O ₁₁ S ₃



Compound	R1	R2	A	Formula
270771	ONa	Na+	-CH2-	C ₁₆ H ₁₄ N ₄ Na ₂ O ₉ S ₂
270774	H	K+	-CH2CH2NHCO-	C ₁₈ H ₁₈ KN ₅ O ₉ S ₂



270775: C25 H26 N6 O12 S3

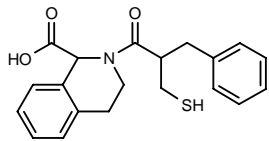
SOURCES – Synphar; Taiho.

REFERENCES

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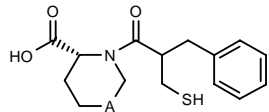
270891

2-(2-Benzyl-3-sulfanylpropionyl)-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic acid



C20 H21 N O3 S; Mol wt: 355.4559

ACTION – A metallo-β-lactamase inhibitor for use in combination with β-lactam antibiotics in the treatment of bacterial infections caused by metallo-β-lactamase-producing strains. It was shown to potentiate the *in vitro* antibacterial activity of meropenem against *Bacteroides fragilis* strain 262, the MIC value of meropenem being reduced from > 128 to 32 µg/ml when given in combination with 8 µg/ml of test compound. Other specifically claimed compounds within this series of heterocyclic amino acid derivatives include the following:



Compound	A	Isomer	Formula
270892	-S-		C ₁₅ H ₁₉ NO ₃ S ₂
270893	-CH ₂ -		C ₁₆ H ₂₁ NO ₃ S
270898	-CH ₂ -	R	C ₁₆ H ₂₁ NO ₃ S
270900	-CH ₂ -	S	C ₁₆ H ₂₁ NO ₃ S

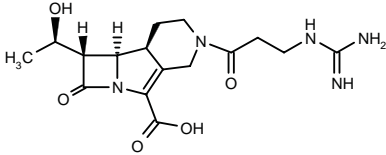
SOURCE – SmithKline Beecham.

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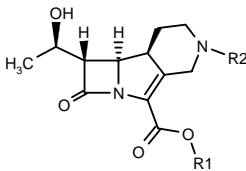
270977

(4a*S*,4b*R*,5*S*)-2-(3-Guanidinopropanoyl)-5-[1(*R*)-hydroxyethyl]-6-oxo-1,2,3,4,4a,4b,5,6-octahydroazeto-[2',1':5,1]pyrrolo[3,4-*c*]pyridine-8-carboxylic acid



C16 H23 N5 O5; Mol wt: 365.3877

ACTION – Tricyclic carbapenem antibiotic from a series of piperidine ring-condensed compounds, wherein the following are also included:



Compound	R1	R2	Formula
270978	H	NH2CH2CH2CO	C ₁₅ H ₂₁ N ₃ O ₅
270979	H	2-NH2-4-thiazolyl-CH2CO	C ₁₇ H ₂₀ N ₄ O ₅ S
270980	K	3-Pyr-CO	C ₁₈ H ₁₈ KN ₃ O ₅
270981	H	CH2CONH2	C ₁₄ H ₁₉ N ₃ O ₅
270982	H	2(S)-azetidiny-CO	C ₁₆ H ₂₁ N ₃ O ₅

SOURCE – Sankyo.

REFERENCES

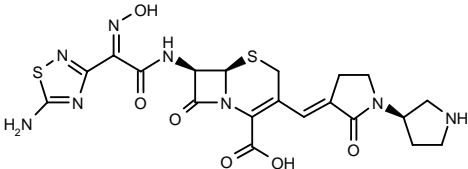
1. Mori, M. and Oida, S. (Sankyo Co., Ltd.) *Piperidine ring condensed carbapenem cpds*. JP 98310582.

RO-63-9141¹⁻¹⁰

268124

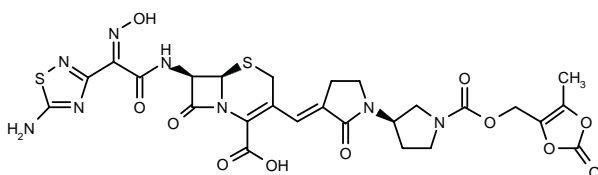
(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(*E*)-1-[3(*R*)-pyrrolidiny]-2-oxopyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylic acid

Ro-63-9141/000



C20 H22 N8 O6 S2; Mol wt: 534.5758

ACTION – Broad-spectrum cephalosporin antibiotic active against both Gram-positive and Gram-negative bacterial strains and particularly against methicillin-resistant staphylococci; MIC₅₀ values of 0.03, 0.015, 0.5, 0.5, 2, 0.25, 1 and 0.5 µg/ml, respectively, were obtained against β-hemolytic streptococci, penicillin-susceptible *Streptococcus pneumoniae*, penicillin-resistant *S. pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *Staphylococcus epidermidis*, methicillin-resistant *S. epidermidis* and *Enterococcus faecalis*. *In vivo*, compound was effective against septicemia in mice caused by MRSA, MSSA, *Streptococcus pyogenes* and penicillin-sensitive and -resistant *S. pneumoniae* (ED₅₀ < 3 mg/kg s.c.), as well as *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter freundii*, *Pseudomonas aeruginosa* and *Proteus mirabilis* (ED₅₀ = 4 mg/kg s.c. or less). Compound penetrated well into the CNS of mice, proving effective in acute meningitis caused by *E. coli*. Due to its poor water solubility, a carbamate prodrug of Ro-63-9141, **Ro-65-5788**, was selected for further development.



Ro-65-5788 [268261]^{1,5}: C₂₆ H₂₆ N₈ O₁₁ S₂

SOURCE – Roche.

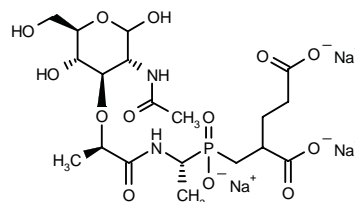
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- Thell, F.-P. et al. *Pharmacokinetics of the cephalosporin Ro 63-9141 in five animal species - Extrapolation to man*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-25.
- Zbinden, R. et al. *Ro 63-9141 (Ro 63), a novel broad-spectrum anti-MRSA pyrrolidinone cephalosporin: Activity against Gram-negative nonfermenters*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-19.

ANTIBACTERIAL DRUGS

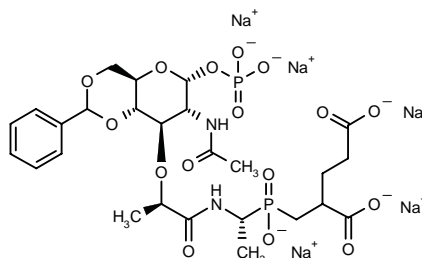
269666

2-[[1(R)-[2(R)-(2-Acetamido-2-deoxy-D-glucopyranos-3-O-yl)propionamido]ethyl](hydroxy)phosphorylmethyl]-glutaric acid trisodium salt

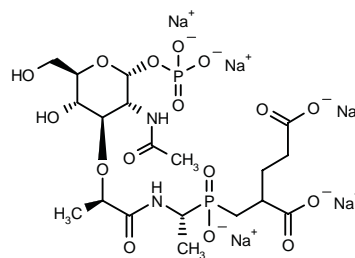


C₁₉ H₃₀ N₂ Na₃ O₁₃ P; Mol wt: 594.391

ACTION – Antibacterial agent that acts by inhibiting UDP-*N*-acetylmuramoylalanine-D-glutamate ligase (Mur D), an enzyme involved in bacterial peptidoglycan biosynthesis. Other specifically claimed compounds include the following:



269667: C₂₆ H₃₃ N₂ Na₅ O₁₆ P₂



269668: C₁₉ H₂₉ N₂ Na₅ O₁₆ P₂

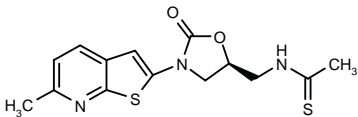
SOURCE – Merck & Co.

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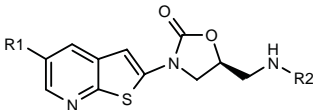
269860

N-[3-(6-Methylthieno[2,3-*b*]pyridin-2-yl)-2-oxooxazolidin-5(*S*)-ylmethyl]thioacetamide



C14 H15 N3 O2 S2; Mol wt: 321.4235

ACTION – Oxazolidinone antibacterial agent with low toxicity and a broad spectrum of activity, especially against Gram-positive bacteria, *Haemophilus influenzae*, anaerobic microorganisms and rapidly growing mycobacteria. Other specifically claimed pyrido-fused thienyl- and furanyl-oxazolidinone derivatives include the following:



Compound	R1	R2	Formula
269861	Me	Ac	C ₁₄ H ₁₅ N ₃ O ₃ S
269862	H	CSMe	C ₁₃ H ₁₃ N ₃ O ₂ S ₂
269863	H	CSNHMe	C ₁₃ H ₁₄ N ₄ O ₂ S ₂
269864	Me	CSMe	C ₁₄ H ₁₅ N ₃ O ₂ S ₂

SOURCE – Bayer.

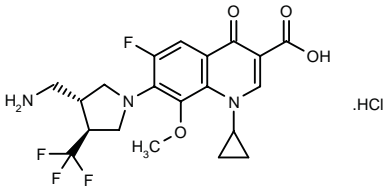
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S-34109

270000

7-[3(*R*)-(Aminomethyl)-4(*S*)-(trifluoromethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride



C20 H21 F4 N3 O4 . HCl; Mol wt: 479.8558

ACTION – Fluoroquinolone antibacterial agent, the more active (3*R*,4*S*)-enantiomer of the racemate S-32730⁺ with a broad spectrum of activity against Gram-positive bacteria including quinolone-resistant *Staphylococcus aureus*, as well as Gram-negative bacteria. Compound was highly effective against both ciprofloxacin (CIP)-susceptible (MIC = 0.008 µg/ml or less) and CIP-resistant *S. aureus* (MIC = 0.5 µg/ml or less), and against two highly CIP- and methicillin-resistant *S. aureus* strains (P8/128 and CR1; MIC = 0.25 and 0.5 µg/ml, respectively). In rats with experimental endocarditis caused by the latter strains, treatment with S-34109 was effective against P8/128 but not against CR1 due to the emergence of resistance to the compound. It also displayed high activity against *Chlamydia pneumoniae* and *Chlamydia*

trachomatis (MIC = 0.03 µg/ml), being 10-fold more active than other quinolones and equieffective to erythromycin.

SOURCE – Kaken.

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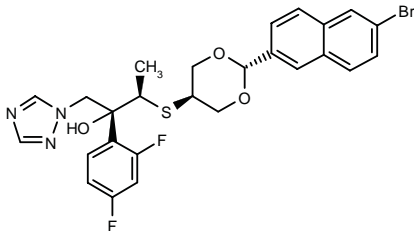
6. Roblin, P.M. and Hammerschlag, M.R. *In vitro activity of a new quinolone, S-34109, against Chlamydia pneumoniae and C. trachomatis*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-75.

*Drug Data Report 1996, 018(01): 0069.

ANTIFUNGAL AGENTS

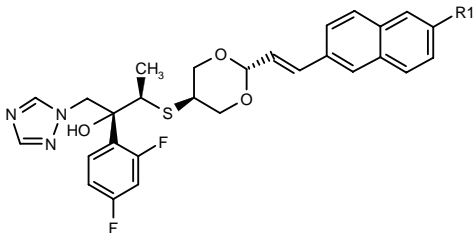
270312

(2*R*,3*R*)-3-[*trans*-2-(6-Bromo-2-naphthyl)-1,3-dioxan-5-ylsulfanyl]-2-(2,4-difluorophenyl)-1-(1,2,4-triazol-1-yl)-2-butanol



C26 H24 Br F2 N3 O3 S; Mol wt: 576.4596

ACTION – Orally active antifungal agent shown to provide 100% protection against lethality in mice inoculated with *Candida albicans* at 14 and 21 days after a dose of 20 mg/kg p.o. at 1, 4 and 24 h after inoculation; for comparison, fluconazole provided only 60-70% protection at the same dose. Within this series of triazole derivatives, the following are also included:



Compound	R1	Formula
270313	Br	C ₂₈ H ₂₆ BrF ₂ N ₃ O ₃ S
270314	OCH2CF2CHF2	C ₃₁ H ₂₈ F ₆ N ₃ O ₄ S

SOURCE – Sankyo.

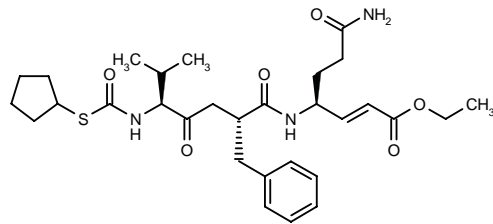
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ANTIVIRAL DRUGS

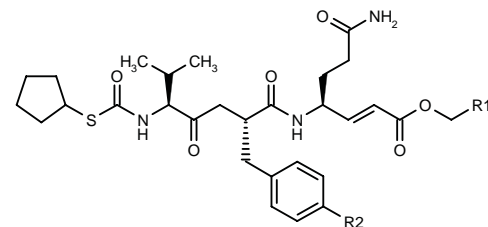
269837

4(S)-[2(R)-Benzyl-5(S)-(cyclopentylsulfanylcarboxamido)-6-methyl-4-oxoheptanoyl]-6-carbamoyl-2(E)-hexenoic acid ethyl ester

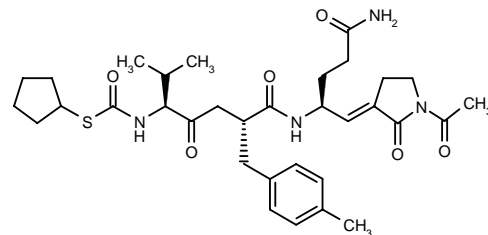


C30 H43 N3 O6 S; Mol wt: 573.7507

ACTION – Antiviral agent that inhibits picornaviral 3C protease and shows potent *in vitro* activity against human rhinovirus serotype 14 (HRV-14) in infected HI-HeLa cells (EC₅₀ = 0.022 μM) and low cytotoxicity against uninfected cells (CC₅₀ > 10 μM). It also protected these cells against infection caused by Coxsackievirus strain A-21 (EC₅₀ = 0.16 μM). Other related compounds include the following:



Compound	R1	R2	Formula
269838	Me	Me	C ₃₁ H ₄₅ N ₃ O ₆ S
269839	Me	F	C ₃₀ H ₄₂ FN ₃ O ₆ S
269841	3-Pyr	F	C ₃₄ H ₄₃ FN ₄ O ₆ S



269840: C33 H46 N4 O6 S

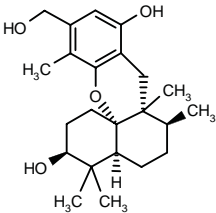
SOURCE – Agouron.

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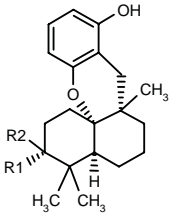
269903

(3*S*,4*aS*,7*S*,7*aR*,13*aS*)-11-(Hydroxymethyl)-4,4,7,7*a*,12-pentamethyl-1,2,3,4,4*a*,5,6,7,7*a*,8-decahydrobenzo-[*d*]xanthene-3,9-diol



C23 H34 O4; Mol wt: 374.5176

ACTION – Antiviral agent for the treatment of influenza A and B virus infection, with potent *in vitro* activity against influenza virus A/WSN/33 (H1N1) in infected MDBK cells (EC₅₀ = 0.008-0.015 μg/ml) and low cytotoxic potential against uninfected cells (CC₅₀ = 25-50 μg/ml). Other representative compounds within this series of benzo-xanthene derivatives include the following:



Compound	R1	R2	Formula
269904	OH	H	C ₂₀ H ₂₈ O ₃
269905	-O-		C ₂₀ H ₂₈ O ₃

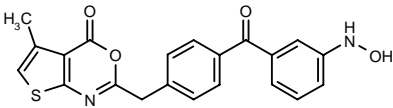
SOURCE – Shionogi.

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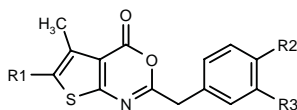
270031

2-[4-[3-(Hydroxyamino)benzoyl]benzyl]-5-methyl-4*H*-thieno[2,3-*d*][1,3]oxazin-4-one



C21 H16 N2 O4 S; Mol wt: 392.4334

ACTION – Antiviral agent for the treatment of infections caused by herpesviruses, especially cytomegalovirus and herpes simplex virus type 2 (HSV-2), that acts by inhibiting herpesvirus protease. Other specifically claimed compounds from this series of 4*H*-3,1-benzoxazin-4-one, 4*H*-thieno[3,2-*d*][1,3]oxazin-4-one and 4*H*-thieno[2,3-*d*][1,3]oxazin-4-one derivatives include the following:



Compound	R1	R2	R3	Formula
270032	Me	3-(HONH)-PhCO	H	C ₂₂ H ₁₈ N ₂ O ₄ S
270033	H	H	3-(HONH)-PhCONH	C ₂₁ H ₁₇ N ₃ O ₄ S
270034	H	H	4-(HONH)-PhCONH	C ₂₁ H ₁₇ N ₃ O ₄ S
270035	H	4-(HONH)-PhCO	H	C ₂₁ H ₁₆ N ₂ O ₄ S

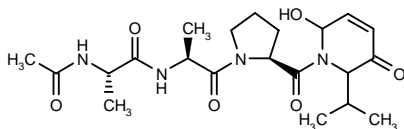
SOURCE – SmithKline Beecham.

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270105

1-(Acetyl-L-alanyl-L-alanyl-L-prolyl)-6-hydroxy-2-isopropyl-1,2,3,6-tetrahydropyridin-3-one



C21 H32 N4 O6; Mol wt: 436.5058

ACTION – Antiviral agent for the treatment of hepatitis C virus infection, human cytomegalovirus (CMV) infection, yellow fever, viral encephalitis, pulmonary emphysema and other related diseases, a potent inhibitor of human and viral serine proteases including CMV protease. In addition, the compound produced about 20% inhibition of porcine pancreatic elastase at a concentration of 17 μ M.

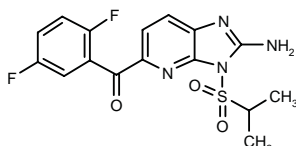
SOURCE – Emory University, Atlanta, GA (US).

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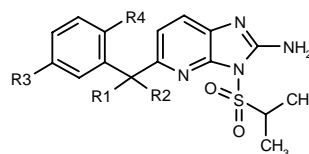
270142

[2-Amino-3-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-5-yl](2,5-difluorophenyl)methanone



C16 H14 F2 N4 O3 S; Mol wt: 380.3736

ACTION – Antiviral agent for the treatment of infections caused by picornaviruses including rhinoviruses and enteroviruses, and hepatitis viruses such as hepatitis C virus (HCV). A representative compound from a series of imidazo[4,5-*b*]pyridines, wherein the following are also included:



Compound	R1,R2	R3	R4	Formula
270143	-O-	H	H	C ₁₆ H ₁₆ N ₄ O ₃ S
270144	-O-	F	H	C ₁₆ H ₁₅ FN ₄ O ₃ S
270145	-(E)-CH(CONHMe)-	F	F	C ₁₉ H ₁₉ F ₂ N ₅ O ₃ S
270146	-(E)-N(OH)-	H	H	C ₁₆ H ₁₇ N ₅ O ₃ S
270147	-(Z)-N(OH)-	H	H	C ₁₆ H ₁₇ N ₅ O ₃ S
270148	-CH(CONHMe)-	H	H	C ₁₉ H ₂₁ N ₅ O ₃ S
270149	-(Z)-CH(CONHMe)-	H	H	C ₁₈ H ₁₉ N ₅ O ₃ S
270151	-(E)-N(OH)-	F	H	C ₁₆ H ₁₆ FN ₅ O ₃ S
270152	-CH2-	F	H	C ₁₇ H ₁₇ FN ₄ O ₂ S
270155	-(E)-CH(Br)-	F	H	C ₁₇ H ₁₆ BrFN ₄ O ₂ S
270157	-(E)-CH(CN)-	F	H	C ₁₈ H ₁₆ FN ₅ O ₂ S
270158	-CH(CONHMe)-	F	H	C ₁₉ H ₂₀ FN ₅ O ₃ S

SOURCE – Lilly.

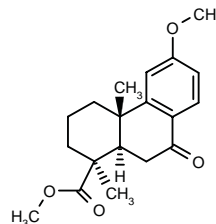
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LY-180299

235956

(1*S*,4*aS*,10*aR*)-6-Methoxy-1,4*a*-dimethyl-9-oxo-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxylic acid methyl ester



C19 H24 O4; Mol wt: 316.3946

ACTION – Antiviral agent active against influenza A/Kawasaki/86 (H1N1) and Ann Arbor/69 and Ann Arbor/1/57 (H2N2) viruses (IC₅₀ = 0.01-0.05 μ g/ml), but not influenza A/WSN/33 (H1N1), H3N2 or influenza B viruses. Compound appears to interact with the neutral pH conformation of influenza A hemagglutinin and to prevent the low-pH-induced change of hemagglutinin to its fusogenic conformation, resulting in inhibition of membrane fusion and thus virus replication.

SOURCE – Lilly.

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2. Hornback, W.J. and Munroe, J.E. (Eli Lilly and Company) *Anti-viral cpds*. EP 806408, WO 9741822.
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4. Staschke, K.A. et al. *A compound derived from podocarpic acid inhibits influenza A virus replication in vitro*. *Antivir Res* 1996, 30(1): Abst 30.

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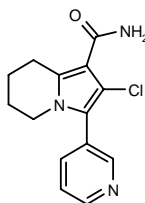
6. Staschke, K.A. et al. *Inhibition of influenza virus hemagglutinin-mediated membrane fusion by a compound related to podocarpic acid*. *Virology* 1998, 248(2): 264.

RPR-CMV-423

268242

2-Chloro-3-(3-pyridinyl)-5,6,7,8-tetrahydroindolizin-1-carboxamide

RPR-111423



C14 H14 Cl N3 O; Mol wt: 275.7376

ACTION – Antiviral agent with potent and selective activity against human cytomegalovirus (HCMV) that appears to have a novel mechanism of action and to target an early stage in the virus replicative cycle, prior to viral DNA synthesis. Compound inhibited the replication of various strains and clinical isolates of HCMV with IC_{50} values of 0.0047-0.046 μ M and was highly active against drug-resistant strains; a high selectivity index was also found. Synergistic activity was observed for combinations of RPR-CMV-423 and ganciclovir, cidofovir and foscarnet.

SOURCE – Rhône-Poulenc Rorer.

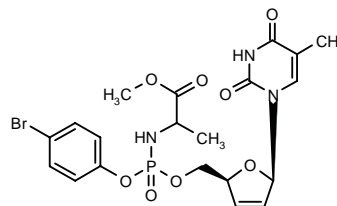
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1. Bacque, E. et al. (Rhône-Poulenc Rorer SA) *Novel use for pyrrole derivs*. WO 9700073.
2. Andrei, G. et al. *Effect of RPR111423 in combination with other antiviral agents in the inhibition of HCMV in vitro*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-109c.
3. Andrei, G. et al. *RPR CMV423 inhibits replication of HCMV at an early step of the virus replicative cycle*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-84.
4. Bodaghi, B. et al. *Inhibition of cytomegalovirus replication in human retinal pigment epithelial cells with RPR CMV423*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-98.
5. Lagneau, L. et al. *In vitro effect of RPR CMV423 on HCMV replication and cytokine production in human bone marrow stromal cells*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-99.
6. Lagneau, L. et al. *In vitro effect of RPR CMV423 on HCMV replication and cytokine production in human bone marrow stromal cells*. *Blood* 1998, 92(10, Suppl. 1, Part 1): Abst 1155.

AIDS MEDICINES

269049

5'-O-[(4-Bromophenoxy)(O-methylalanino)phosphoryl]-3'-deoxy-2',3'-dideohydrothymidine



C20 H23 Br N3 O8 P; Mol wt: 544.2927

ACTION – Antiviral agent for AIDS found to inhibit HIV replication in peripheral blood mononuclear cells, as measured by assays of p24 production (IC_{50} = 22 nM) and reverse transcriptase activity (IC_{50} = 42 nM), and in thymidine kinase-deficient CEM cells (IC_{50} = 44 and 57 nM, respectively); compound did not show any detectable cytotoxicity in either cell line at concentrations as high as 10 μ M. It inhibited the replication of HIV-2 and zidovudine-resistant HIV-1 strains at submicromolar concentrations.

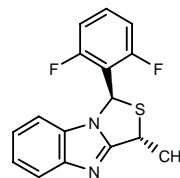
SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

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2. Vig, R. et al. *D4T-5'-[p-Bromophenyl methoxyalaninyl phosphate] as a potent and non-toxic anti-human immunodeficiency virus agent*. *Antivir Chem Chemother* 1998, 9(5): 445.

269053

(1*R*,3*R*)-1-(2,6-Difluorophenyl)-3-methyl-3*H*-1,3-thiazolo-[3,4-*a*]benzimidazole



C16 H12 F2 N2 S; Mol wt: 302.3468

White powder, m.p. 154-6 °C.

ACTION – Anti-HIV agent, an analogue of TBZ that inhibits HIV-1 replication in MT-4 cells with an EC_{50} of 0.3 μ g/ml, but is devoid of activity against HIV-2 (EC_{50} > 11 μ g/ml) and shows relatively low cytotoxicity (CC_{50} = 11 μ g/ml). Compound exhibited comparable activity against HIV-1IIB and RF strains whereas NDK strains were less sensitive.

SOURCES – Katholieke Universiteit Leuven, Leuven (BE); Università degli Studi di Messina, Messina (IT).

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1. Chimirri, A. et al. *Synthesis, structure and in vitro anti-human immunodeficiency virus activity of novel 3-methyl-1H,3H-thiazolo[3,4-a]benzimidazoles*. *Antivir Chem Chemother* 1998, 9(5): 431.

269850

ACTION – Noninfectious, protease-defective HIV-1 particles obtained from L-2 cells containing mutations at the Nef, Env gp41, Env gp120, Pol protease or Vpr proteins, or combinations thereof, potentially useful as immunogens for vaccination against or treatment of AIDS. Antibodies against these proteins are also claimed.

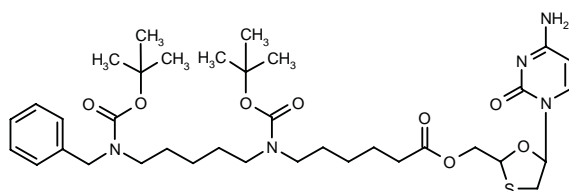
SOURCE – Immune Response.

REFERENCES

1. Luftig, R.B. (The Immune Response Corp.) *Non-infectious, protease defective HIV particles and nucleic acid molecules encoding therefor*. WO 9844945.

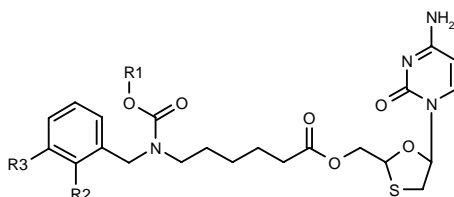
269877

1-[2-[6-[N-[5-[N-Benzyl-N-(*tert*-butoxycarbonyl)-amino]pentyl]-N-(*tert*-butoxycarbonyl)amino]-hexanoyloxymethyl]-1,3-oxathiolan-5-yl]cytosine

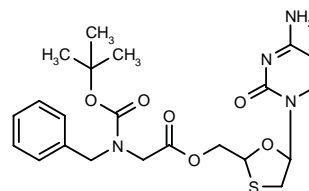


C36 H55 N5 O8 S; Mol wt: 717.9235

ACTION – Antiviral agent for AIDS, an inhibitor of reverse transcriptase with potent anti-HIV activity in MT-4 cells infected by HIV-1 strain BRU ($IC_{50} = 0.001\text{--}0.005\ \mu\text{M}$) and in human macrophages infected by the macrophage-trophic HIV-1 PAR strain ($IC_{50} < 10\ \mu\text{M}$). Within this series of pyrimidinone-1,3-oxathiolane derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269878	t-Bu	H	H	C ₂₆ H ₃₆ N ₄ O ₆ S
269879	t-Bu	H	CF ₃	C ₂₇ H ₃₅ F ₃ N ₄ O ₆ S
269880	t-Bu	CF ₃	H	C ₂₇ H ₃₅ F ₃ N ₄ O ₆ S
269881	Et	H	H	C ₂₄ H ₃₂ N ₄ O ₆ S



269882: C22 H28 N4 O6 S

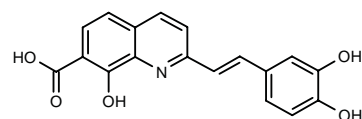
SOURCES – INSERM; Zambon.

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1. Pellacini, F. et al. (Zambon Group SpA;INSERM [Institut National de la Sante et de la Recherche Medicale]) *Pyrimidinone-1,3-oxathiolane derivs. with antiviral activity*. WO 9843972.

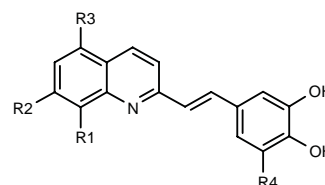
269979

2-[2-(3,4-Dihydroxyphenyl)vinyl]-8-hydroxyquinoline-7-carboxylic acid



C18 H13 N O5; Mol wt: 323.3027

ACTION – Antiviral agent for AIDS that acts by selectively inhibiting HIV integrase, as demonstrated in several *in vitro* tests by inhibition of strand transfer and HIV integrase substrate cleavage. Compound was shown to be devoid of reverse transcriptase-inhibitory activity. Antiviral activity was demonstrated in HIV-1-infected CEM cells ($IC_{50} = 4\text{--}20\ \mu\text{M}$), and no cytotoxicity was observed at concentrations up to $100\ \mu\text{M}$. Other specifically claimed compounds from this series of quinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
269980	H	H	H	H	C ₁₇ H ₁₃ NO ₂
269981	OH	H	H	H	C ₁₇ H ₁₃ NO ₃
269982	OH	CO ₂ ⁻ Na ⁺	H	H	C ₁₈ H ₁₂ NNaO ₅
269983	OH	CN	H	H	C ₁₈ H ₁₂ N ₂ O ₃
269984	OH	CO ₂ H	H	OH	C ₁₈ H ₁₃ NO ₆
269985	H	CO ₂ H	CO ₂ H	H	C ₁₉ H ₁₃ NO ₆

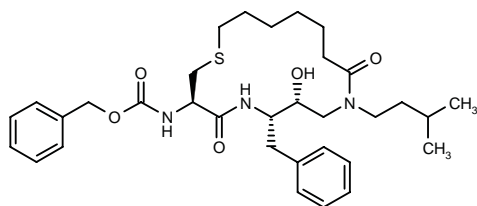
SOURCE – CNRS.

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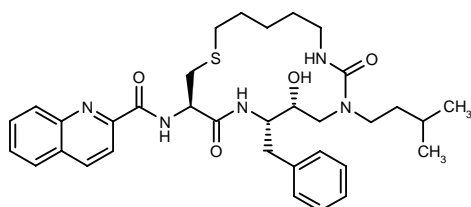
270226

(3*R*,6*S*,7*R*)-*N*-[6-Benzyl-7-hydroxy-9-(3-methylbutyl)-4,10-dioxo-1-thia-5,9-diazacyclohexadec-3-yl]carbamic acid benzyl ester



C33 H47 N3 O5 S; Mol wt: 597.8163

ACTION – Antiviral agent for AIDS, an inhibitor of retroviral proteases, particularly HIV protease (IC_{50} = 140 nM). Another representative compound within this series of *N*-heterocyclic-containing macrocyclic hydroxyethylamine derivatives is:



270233: C34 H45 N5 O4 S

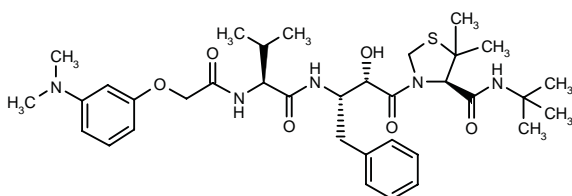
SOURCE – Monsanto.

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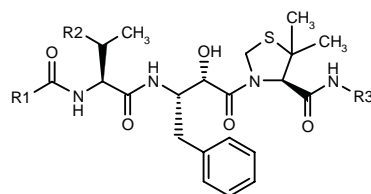
270447

N-*tert*-Butyl-3-[3(*S*)-[*N* α -[2-[3-(dimethylamino)phenoxy]acetyl]-*L*-valylamino]-2(*S*)-hydroxy-4-phenylbutyl]-5,5-dimethylthiazolidine-4(*R*)-carboxamide



C35 H51 N5 O6 S; Mol wt: 669.8829

ACTION – Antiviral agent for AIDS, a potent HIV protease inhibitor (96.0% inhibition at 50 nM) with potent activity against HIV in CEM-SS cells (EC_{50} = 10 ng/ml) and low cytotoxicity in uninfected cells (TC_{50} > 1.0 μ g/ml). It showed excellent oral bioavailability in rats (89%). Other tripeptide compounds include the following:



Compound	R1	R2	R3	Formula
270448	7-MeO-2-benzofuryl	Me	2-Me-PhCH ₂	C ₃₉ H ₄₆ N ₄ O ₇ S
270449	OMe	Me	2-Me-PhCH ₂	C ₃₁ H ₄₂ N ₄ O ₆ S
270450	3-N(Me)2-PhOCH ₂	H	t-Bu	C ₃₄ H ₄₉ N ₅ O ₆ S

SOURCE – Japan Energy.

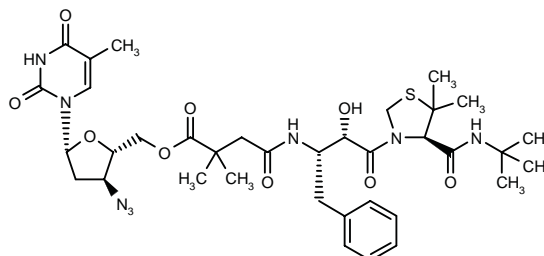
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KNI-684

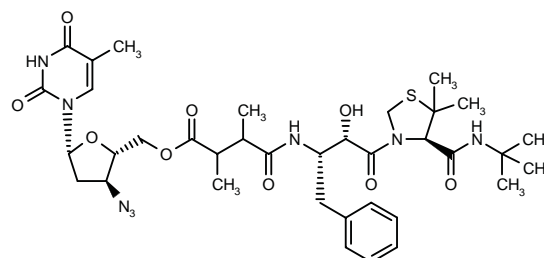
270153

3'-Azido-5'-*O*-[3-[*N*-[1(*S*)-benzyl-2(*S*)-[4(*R*)-(*N*-*tert*-butylcarbonyl)-5,5-dimethylthiazolidin-3-ylcarbonyl]-2-hydroxyethyl]carbonyl]-2,2-dimethylpropionyl]-3'-deoxythymidine



C36 H50 N8 O9 S; Mol wt: 770.904

ACTION – Anti-HIV conjugate of the HIV protease inhibitor KNI-413 with the reverse transcriptase inhibitor zidovudine that retains good protease-inhibitory activity (41% at 5 μ M) and is about 6-fold more potent than zidovudine in inhibiting HIV reverse transcriptase (EC_{50} = 19 nM vs. 126 nM). Another conjugate contains the protease inhibitor KNI-549:



KNI-685 [270154]: C36 H50 N8 O9 S

SOURCE – Kyoto Pharmaceutical University, Kyoto (JP).

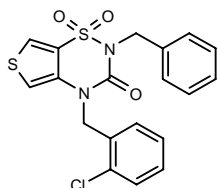
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QM-96625¹

269360

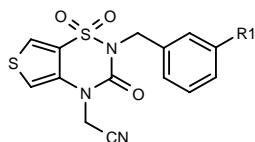
2-Benzyl-4-(2-chlorobenzyl)-2,3-dihydro-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine-3-one 1,1-dioxide



C19 H15 Cl N2 O3 S2; Mol wt: 418.9235

M.p. 156-8 °C.

ACTION – Non-nucleoside reverse transcriptase inhibitor with potent anti-HIV-1 activity in infected MT-4 cells (EC_{50} = 90 nM) and very low cytotoxicity in uninfected cells (CC_{50} > 340 μ M; selectivity index > 3778). Other lead compounds within this series of trioxo-thieno-thiadiazines (TTDs) include the following:



Compound	R1	Formula
QM-96539 [269361] ¹	Cl	C ₁₄ H ₁₀ ClN ₂ O ₃ S ₂
QM-96639 [269362] ^{1,2}	F	C ₁₄ H ₁₀ FN ₂ O ₃ S ₂

SOURCES – CSIC, Madrid (ES); Katholieke Universiteit Leuven, Leuven (BE).

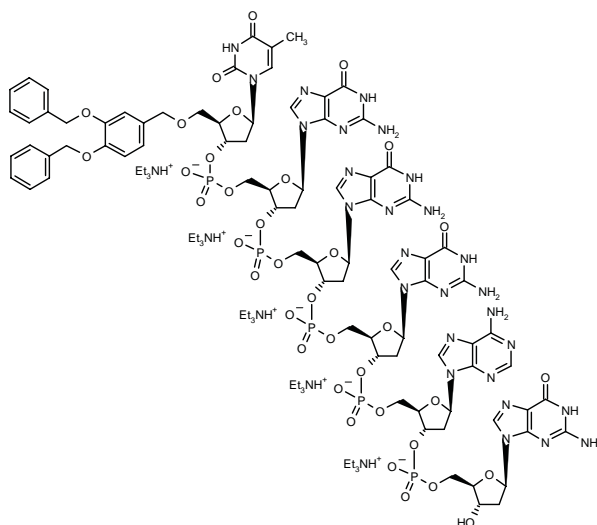
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2. Witvrouw, M. et al. *1,1,3-Trioxo-2H,4H-thieno[3,4-*e*][1,2,4]thiadiazine (TTD) derivatives: A new class of nonnucleoside human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors with anti-HIV-1 activity*. Antimicrob Agents Chemother 1998, 42(3): 618.

S-1401

268331

5'-O-[3,4-Bis(phenylmethoxy)benzyl]thymidyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyguanosine penta(*N,N*-diethylethanamine) inner salt



C81 H87 N27 O36 P5 . 5 C6 H16 N; Mol wt: 2680.598

ACTION – Antiviral agent for AIDS, a substituted hexadeoxyribonucleotide that is able to inhibit HIV-1IIB-induced cytopathicity in MT-4 cells (IC_{50} = 0.37 μ M) with low cytotoxicity (CC_{50} > 40 μ M). Compound appears to interfere with both cell–cell and virus–cell transmission of HIV-1 by interacting with both the V3 loop and the CD4 binding site on viral gp120.

SOURCE – Sankyo.

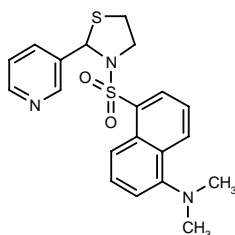
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2. Hotoda, H. et al. *Biologically active oligodeoxyribonucleotides. 10: Anti-HIV-1 activity and stability of modified hexanucleotides containing glycerol-skeleton*. Nucleosides Nucleotides 1998, 17(1-3): 243.
3. Hotoda, H. et al. *Biologically active oligodeoxyribonucleotides. 5: 5'-End-substituted d(TGGGAG) possesses anti-human immunodeficiency virus type 1 activity by forming a G-quadruplex structure*. J Med Chem 1998, 41(19): 3655.
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YHI-1

269052

3-[5-(Dimethylamino)naphthyl-1-ylsulfonyl]-2-(3-pyridinyl)thiazolidine



C20 H21 N3 O2 S2; Mol wt: 399.5369

ACTION – Anti-HIV agent, a synthetic analogue of D-cysteinolic acid, isolated from sardines, that inhibits HIV-1 reverse transcriptase in various cell lines such as MT-4 cells, peripheral blood mononuclear cells and MAGI-CCR5 cells with EC_{50} values of 3.35, 10.23 and 4.61 μ M, respectively; it showed low cytotoxicity in MT-4 cells (CC_{50} = 1827.45 μ M). Compound failed to inhibit HIV-2 or non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant strains of HIV-1, showing a pattern of antiviral activity similar to nevirapine. Its activity appears to be due to a metabolite that acts intracellularly as an NNRTI, and it is considered a good candidate for further development.

SOURCES – Nippon Suisan; Taisho.

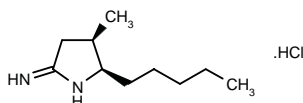
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2. Nakajima, H. and Kanbara, K. (Nippon Suisan Co., Ltd.) *Thiazolidine cpds. having anti-HIV activity.* JP 97249565.
3. Premanathan, M. et al. 3-(5-Dimethylamino-1-naphthalenesulfonyl)-2-(3-pyridyl)thiazolidine (YHI-1) selectively inhibits human immunodeficiency virus type 1. *Antivir Chem Chemother* 1998, 9(5): 423.

TREATMENT OF SEPTIC SHOCK

268326

(+)-*cis*-4-Methyl-5-pentylpyrrolidin-2-imine hydrochloride



C10 H20 N2 . HCl; Mol wt: 204.7429

ACTION – Potent inhibitor of human inducible nitric oxide synthase (iNOS; IC_{50} = 0.25 μ M) with high selectivity versus human endothelial and neuronal NOS (897- and 13-fold, respectively). In mice, compound inhibited lipopolysaccharide (LPS)-induced systemic expression of iNOS, with an ED_{50} of about 3 mg/kg p.o., whereas it did not decrease blood pressure at up to 10 mg/kg i.v. in conscious animals.

SOURCE – Searle.

REFERENCES

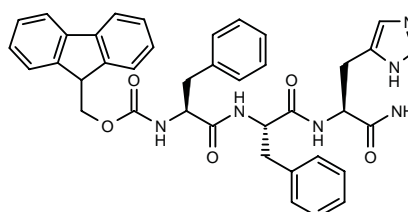
1. Hagen, T.J. et al. 2-Iminopyrrolidines as potent and selective inhibitors of human inducible nitric oxide synthase. *J Med Chem* 1998, 41(19): 3675.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

269038

N-(Fluoren-9-ylmethoxycarbonyl)-L-phenylalanyl-L-phenylalanyl-L-histidinamide



C39 H38 N6 O5; Mol wt: 670.7662

ACTION – Tripeptide with macrophage migration-enhancing activity; at a concentration of 0.1 μ M, it significantly enhanced the migration of rabbit alveolar macrophages. Potentially useful as an antiinflammatory drug.

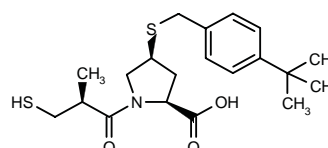
SOURCE – Tanabe.

REFERENCES

1. Nunami, K. et al. *Design of novel tripeptides with macrophage migration-enhancing activity.* *Bioorg Med Chem Lett* 1998, 8(18): 2517.

269578

4(*S*)-(4-*tert*-Butylbenzylsulfonyl)-*N*-[2(*S*)-methyl-3-sulfonylpropionyl]-*L*-proline



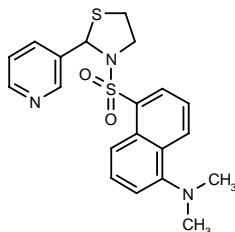
C20 H29 N O3 S2; Mol wt: 395.5851

ACTION – Inhibitor of LTA_4 hydrolase (IC_{50} = 0.031 μ M using guinea pig lung homogenates as the source of the enzyme), potentially useful for the treatment of inflammatory conditions such as rheumatoid arthritis, psoriasis, gout and cystic fibrosis. Other representative compounds include the following:

YHI-1

269052

3-[5-(Dimethylamino)naphthyl-1-ylsulfonyl]-2-(3-pyridinyl)thiazolidine



C20 H21 N3 O2 S2; Mol wt: 399.5369

ACTION – Anti-HIV agent, a synthetic analogue of D-cysteinolic acid, isolated from sardines, that inhibits HIV-1 reverse transcriptase in various cell lines such as MT-4 cells, peripheral blood mononuclear cells and MAGI-CCR5 cells with EC_{50} values of 3.35, 10.23 and 4.61 μ M, respectively; it showed low cytotoxicity in MT-4 cells (CC_{50} = 1827.45 μ M). Compound failed to inhibit HIV-2 or non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant strains of HIV-1, showing a pattern of antiviral activity similar to nevirapine. Its activity appears to be due to a metabolite that acts intracellularly as an NNRTI, and it is considered a good candidate for further development.

SOURCES – Nippon Suisan; Taisho.

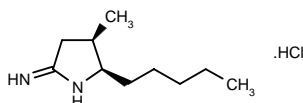
REFERENCES

1. Iwata, M. et al. (Taisho Pharmaceutical Co., Ltd.; Nippon Suisan Co., Ltd.) *Thiazolidine derivs.* JP 91275678.
2. Nakajima, H. and Kanbara, K. (Nippon Suisan Co., Ltd.) *Thiazolidine cpds. having anti-HIV activity.* JP 97249565.
3. Premanathan, M. et al. *3-[5-(Dimethylamino-1-naphthalenesulfonyl)-2-(3-pyridyl)thiazolidine (YHI-1) selectively inhibits human immunodeficiency virus type 1.* Antivir Chem Chemother 1998, 9(5): 423.

TREATMENT OF SEPTIC SHOCK

268326

(+)-*cis*-4-Methyl-5-pentylpyrrolidin-2-imine hydrochloride



C10 H20 N2 . HCl; Mol wt: 204.7429

ACTION – Potent inhibitor of human inducible nitric oxide synthase (iNOS; IC_{50} = 0.25 μ M) with high selectivity versus human endothelial and neuronal NOS (897- and 13-fold, respectively). In mice, compound inhibited lipopolysaccharide (LPS)-induced systemic expression of iNOS, with an ED_{50} of about 3 mg/kg p.o., whereas it did not decrease blood pressure at up to 10 mg/kg i.v. in conscious animals.

SOURCE – Searle.

REFERENCES

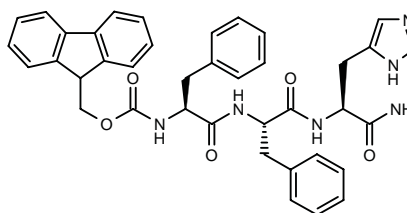
1. Hagen, T.J. et al. *2-Iminopyrrolidines as potent and selective inhibitors of human inducible nitric oxide synthase.* J Med Chem 1998, 41(19): 3675.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

269038

N-(Fluoren-9-ylmethoxycarbonyl)-L-phenylalanyl-L-phenylalanyl-L-histidinamide



C39 H38 N6 O5; Mol wt: 670.7662

ACTION – Tripeptide with macrophage migration-enhancing activity; at a concentration of 0.1 μ M, it significantly enhanced the migration of rabbit alveolar macrophages. Potentially useful as an antiinflammatory drug.

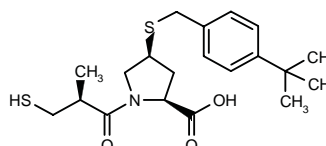
SOURCE – Tanabe.

REFERENCES

1. Nunami, K. et al. *Design of novel tripeptides with macrophage migration-enhancing activity.* Bioorg Med Chem Lett 1998, 8(18): 2517.

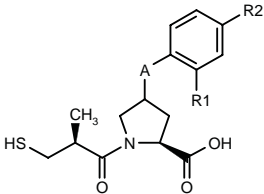
269578

4(*S*)-(4-*tert*-Butylbenzylsulfonyl)-*N*-[2(*S*)-methyl-3-sulfonylpropionyl]-L-proline



C20 H29 N O3 S2; Mol wt: 395.5851

ACTION – Inhibitor of LTA_4 hydrolase (IC_{50} = 0.031 μ M using guinea pig lung homogenates as the source of the enzyme), potentially useful for the treatment of inflammatory conditions such as rheumatoid arthritis, psoriasis, gout and cystic fibrosis. Other representative compounds include the following:



Compound	R1	R2	A	Isomer	Formula
269579	Me	H	-SCH2-	S	C ₁₇ H ₂₃ NO ₃ S ₂
269580	H	i-Pr	-SCH2-	S	C ₁₉ H ₂₇ NO ₃ S ₂
269581	H	i-Pr	-SCH2CH2-	S	C ₂₀ H ₂₉ NO ₃ S ₂
269582	H	i-Pr	-SCH2-	R	C ₁₉ H ₂₇ NO ₃ S ₂
269583	H	i-Pr	-OCH2-	R	C ₁₉ H ₂₇ NO ₄ S
269584	H	SMe	-SCH2-	S	C ₁₇ H ₂₃ NO ₃ S ₃
269585	H	C6H13	-SCH2-	S	C ₂₂ H ₃₃ NO ₃ S ₂

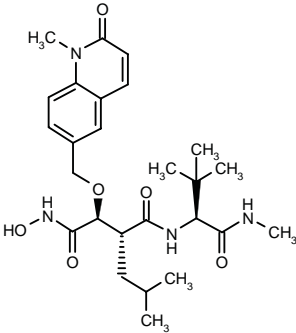
SOURCE – Santen.

REFERENCES

1. Horiuchi, M. et al. (Santen Pharmaceutical Co., Ltd.) *Leukotriene A4 hydrolase inhibitors*. JP 98265456, WO 9843954.

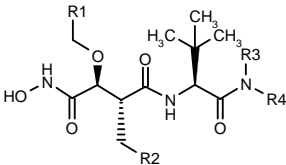
269624

N²-[4-(Hydroxyamino)-2(*R*)-isobutyl-3(*S*)-(1-methyl-2-oxo-1,2-dihydroquinolin-6-ylmethoxy)succinyl]-*N*^{1,3}-dimethyl-L-valinamide



C26 H38 N4 O6; Mol wt: 502.6082

ACTION – Inhibitor of the production of tumor necrosis factor (TNF) and matrix metalloproteinases, claimed for use in the treatment of conditions such as arthritis, tumor metastasis, osteoporosis, adult respiratory distress syndrome, multiple sclerosis and cirrhosis. Within this series of hydroxamic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
269625	1-Me-2-oxo-1,2-dihydro-6-quinoliny	i-Pr	CH2CH2-N(Me)2	H	C ₂₉ H ₄₅ N ₅ O ₆
269626	8-quinoliny	i-Pr	Me	Me	C ₂₆ H ₃₈ N ₄ O ₅
269627	4-oxo-3,4-dihydro-6-quinazoliny	i-Pr	Me	H	C ₂₄ H ₃₅ N ₅ O ₆
269628	2-Me-4-oxo-3,4-dihydro-6-quinazoliny	CH2CH2-OCH2Ph	Me	H	C ₃₁ H ₄₁ N ₅ O ₇
269629	5-quinoxaliny	i-Pr	Me	H	C ₂₄ H ₃₅ N ₅ O ₅

Compound	R1	R2	R3	R4	Formula
269630	1-Me-2,3-dioxo-5-indoliny	i-Pr	Me	H	C ₂₅ H ₃₆ N ₄ O ₇
269631	4-Me-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl	i-Pr	Me	H	C ₂₅ H ₃₈ N ₄ O ₇
269632	2-Me-5-benzothiazoly	i-Pr	Me	H	C ₂₄ H ₃₆ N ₄ O ₅ S

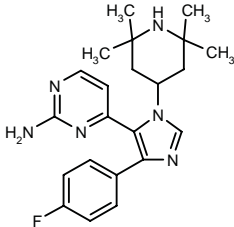
SOURCE – Zeneca.

REFERENCES

1. Bird, T.G.C. (Zeneca Ltd.) *Hydroxamic acids substd. by heterocycles useful for inhibition of tumor necrosis factor*. WO 9843959.

269833

4-[4-(4-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperidin-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine



C22 H27 F N6; Mol wt: 394.4953

ACTION – Antiinflammatory agent, a potent inhibitor of p38 MAP kinase with potential in the treatment of arthritis.

SOURCE – SmithKline Beecham.

REFERENCES

1. Adams, J.L. and Boehm, J.C. *Imidazole cpds., use and process of making*. US 5593991.

2. Adams, J.L. et al. (SmithKline Beecham Corp.) *Pyridyl imidazole cpds. and compsns*. US 5670527.

3. Adams, J.L. et al. (SmithKline Beecham plc) *Certain 1,4,5-tri-substd. imidazole cpds. useful as cytokine*. EP 809499, JP 98512555, US 5593992, WO 9621452.

4. Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries*. EP 889888, WO 9735856.

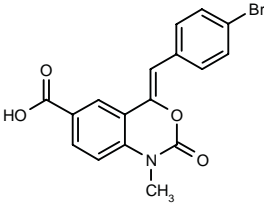
5. Horowitz, D. and King, A.G. (SmithKline Beecham Corp.) *Methods for reversibly inhibiting myelopoiesis in mammalian tissue*. WO 9816230.

6. Sisko, J. (SmithKline Beecham plc) *Novel synthesis*. WO 9723479.

7. Sisko, J. *A one-pot synthesis of 1-(2,2,6,6-tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-amino-4-pyrimidinyl)imidazole: A potent inhibitor of p38 MAP kinase*. J Org Chem 1998, 63(13): 4529.

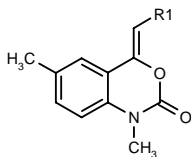
269853

(*Z*)-4-(4-Bromobenzylidene)-1-methyl-2-oxo-2,4-dihydro-1*H*-3,1-benzoxazine-6-carboxylic acid



C17 H12 Br N O4; Mol wt: 374.1888

ACTION – Antiinflammatory and antiarthritic agent proven able to prevent collagen-induced arthritis in mice by about 63% at a dose of 50 mg/kg/day x 44 days p.o. Within this series of 4-arylmethylene-1,4-dihydro-2H-azine derivatives, the following are also included:



Compound	R1	Formula
269854	Ph	C ₁₇ H ₁₅ NO ₂
269855	4-MeO-Ph	C ₁₈ H ₁₇ NO ₃
269856	2-quinolinyl	C ₂₀ H ₁₆ N ₂ O ₂

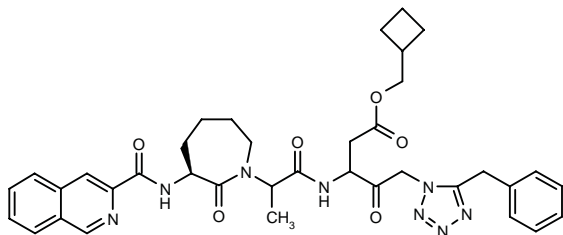
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Nakatsuka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *4-Arylmethylene-1,4-dihydro-2H-azine derivs.* WO 9842688.

269858

5-(5-Benzyltetrazol-1-yl)-3-[2-[3(S)-(isoquinolin-3-ylcarboxamido)-2-oxoperhydroazepin-1-yl]propion-amido]-4-oxopentanoic acid cyclobutylmethyl ester



C37 H42 N8 O6; Mol wt: 694.7888

ACTION – Antiinflammatory and antiarthritic agent, an inhibitor of IL-1 β -converting enzyme (ICE) representative of a series of tetrazole derivatives.

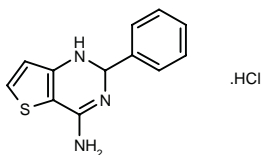
SOURCE – Ono.

REFERENCES

1. Ohmoto, K. et al. (Ono Pharmaceutical Co., Ltd.) *Tetrazole derivs.* JP 98251295.

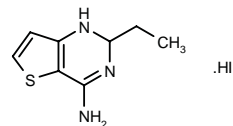
269965

2-Phenyl-1,2-dihydrothieno[3,2-d]pyrimidine-4-amine hydrochloride

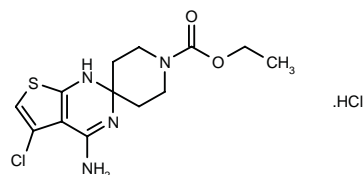


C12 H11 N3 S . HCl; Mol wt: 265.7668

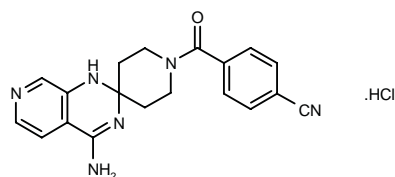
ACTION – An inhibitor of inducible nitric oxide synthase (iNOS) potentially useful for the treatment or prevention of inflammatory disorders such as rheumatoid arthritis and asthma, as well as pain. A representative compound from a series of aminopyridine derivatives, wherein the following are also specifically claimed:



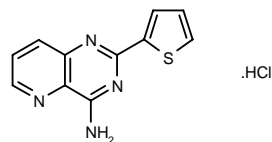
269966: C8 H11 N3 S . HI



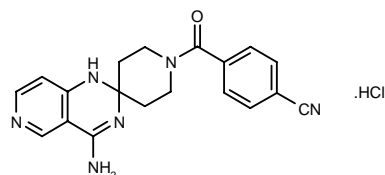
269967: C13 H17 Cl N4 O2 S . HCl



269968: C19 H18 N6 O . HCl



269969: C11 H8 N4 S . HCl



269970: C19 H18 N6 O . HCl

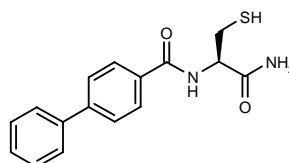
SOURCE – Astra.

REFERENCES

1. McInally, T. and Tinker, A. (Astra Pharmaceuticals Ltd.;Astra AB) *Compounds.* WO 9845294.

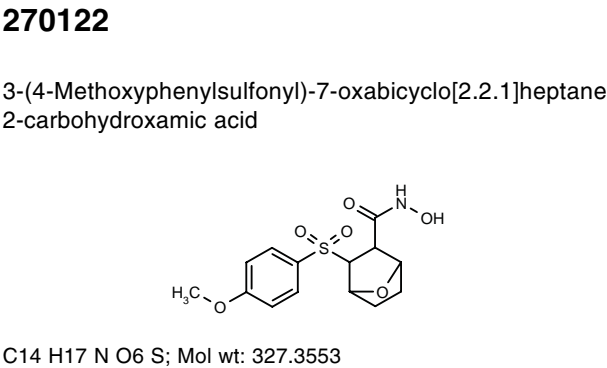
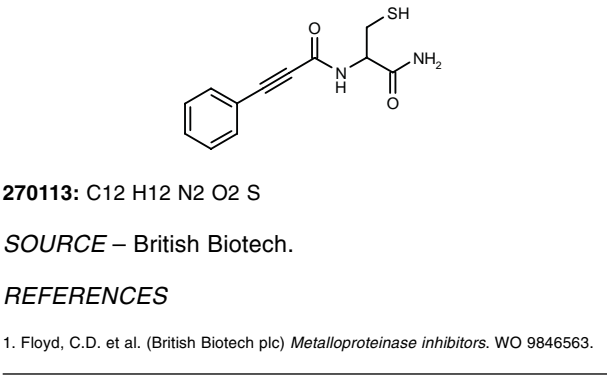
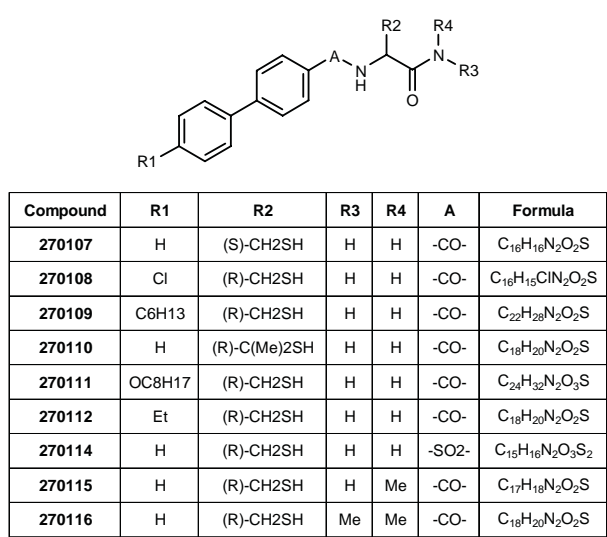
270106

N α -(Biphenyl-4-ylcarbonyl)-L-cysteinamide

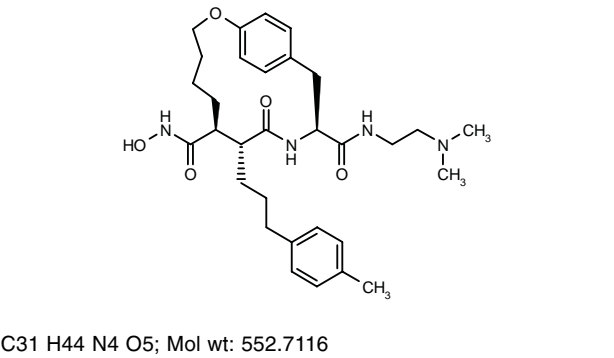
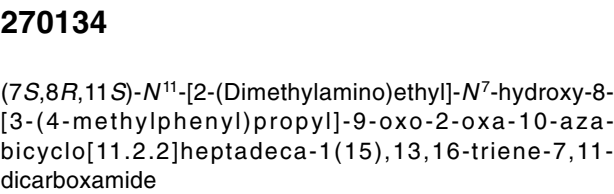
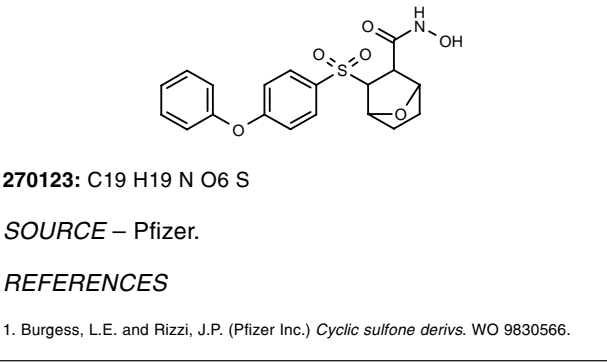


C16 H16 N2 O2 S; Mol wt: 300.3804

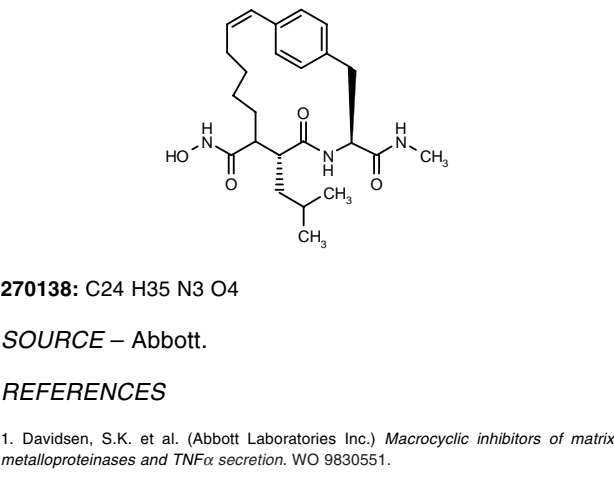
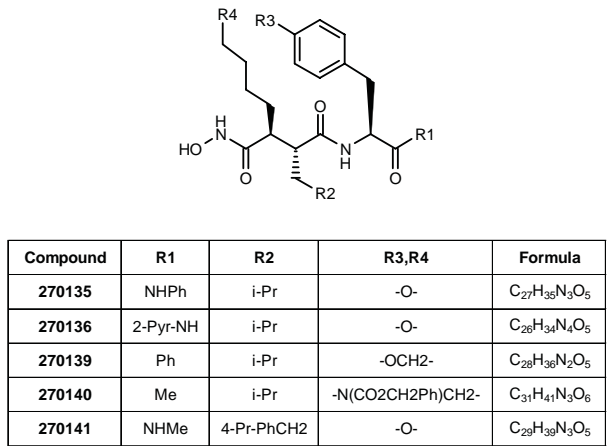
ACTION – Antiarthritic and antiinflammatory agent, an inhibitor of matrix metalloproteinases including collagenase and stromelysin. Other exemplified compounds include the following:



ACTION – Inhibitor of matrix metalloproteinases (MMPs) and/or the production of tumor necrosis factor (TNF), with potential in the treatment of diseases where MMPs or TNF are involved such as arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, septic shock and AIDS. Another exemplified compound from this series of cyclic sulfone derivatives is:

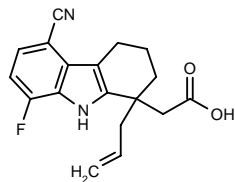


ACTION – Inhibitor of matrix metalloproteinases (MMPs) such as stromelysin (IC₅₀ = 0.56 nM) and the production of tumor necrosis factor-α (TNF-α), with potential in the treatment of diseases where MMPs and/or TNF-α are involved such as arthritis, osteoporosis, periodontitis, ulceration, cancer, asthma, septic shock and inflammatory bowel disease. Other macrocyclic compounds include the following:



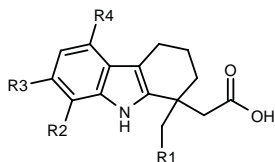
270212

2-(1-Allyl-5-cyano-8-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)acetic acid



C18 H17 F N2 O2; Mol wt: 312.3423

ACTION – Agent for the treatment of inflammatory disorders such as arthritis and Alzheimer’s disease, and of certain types of cancer such as colorectal cancer, a potent inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated using recombinant human enzyme (IC₅₀ = 0.1 μM) and purified sheep COX-1 (93% inhibition at 10 μM). Other specifically claimed pyranoindole and tetrahydrocarbazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
270213	Et	F	H	CN	C ₁₈ H ₁₉ FN ₂ O ₂
270214	vinyl	Me	H	CN	C ₁₉ H ₂₀ N ₂ O ₂
270215	Et	Me	H	CN	C ₁₉ H ₂₂ N ₂ O ₂
270216	Et	CONH2	H	CN	C ₁₉ H ₂₁ N ₃ O ₃
270217	Et	H	H	CN	C ₁₈ H ₂₀ N ₂ O ₂
270218	vinyl	CN	H	CN	C ₁₉ H ₁₇ N ₃ O ₂
270219	Et	CN	H	CN	C ₁₉ H ₁₉ N ₃ O ₂
270220	Et	H	CN	H	C ₁₈ H ₂₀ N ₂ O ₂

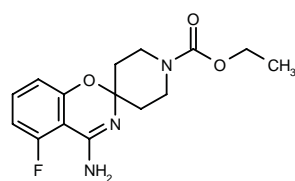
SOURCE – American Home Products.

REFERENCES

1. Failli, A.A. et al. (American Home Products Corp.) *Pyranoindole and tetrahydro-carbazole inhibitors of COX-2*. US 5830911.

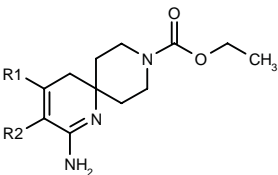
270326

4-Amino-5-fluorospiro[2*H*-1,3-benzoxazine-2,4'-piperidine]-1'-carboxylic acid ethyl ester



C15 H18 F N3 O3; Mol wt: 307.3232

ACTION – Antiinflammatory and analgesic agent, an inhibitor of nitric oxide synthase, preferably the inducible isoform (iNOS; IC₅₀ < 25 μM). Potentially useful for the treatment or prophylaxis of inflammatory disorders such as rheumatoid arthritis or asthma, and pain. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
270327	-SCH=CH-		C ₁₄ H ₁₉ N ₃ O ₂ S
270328	-CH=CHS-		C ₁₄ H ₁₉ N ₃ O ₂ S

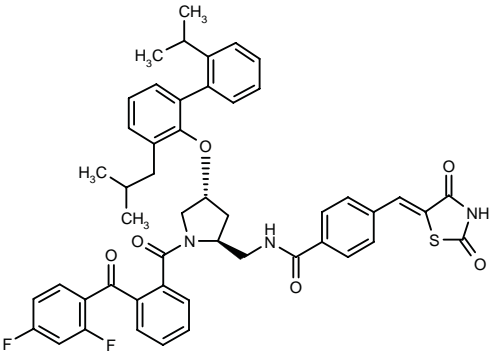
SOURCE – Astra.

REFERENCES

1. Hamley, P. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Compounds*. WO 9846611.

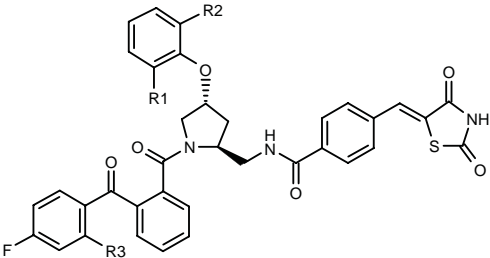
270477

N-[1-[2-(2,4-Difluorobenzoyl)benzoyl]-4(*R*)-(3-isobutyl-2'-isopropylbiphenyl-2-yloxy)pyrrolidin-2(*S*)-ylmethyl]-4-[(*Z*)-2,4-dioxothiazolidin-5-ylidenemethyl]benzamide

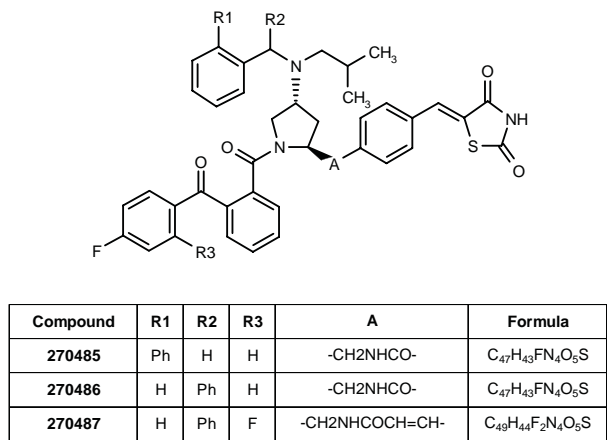
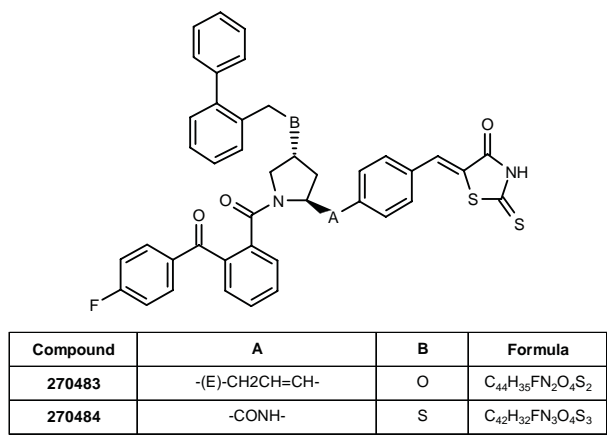


C49 H45 F2 N3 O6 S; Mol wt: 841.9715

ACTION – An inhibitor of cytosolic phospholipase A₂ (cPLA₂; IC₅₀ = 0.0022 μM) proven to inhibit IL-1-stimulated PGE₂ production in human fibroblasts (IC₅₀ = 0.24 μM). Potentially useful in the treatment or prevention of rheumatoid arthritis, asthma, allergic rhinitis, ulcerative colitis, ischemia–reperfusion disorders and psoriasis. Other compounds from this series of pyrrolidine derivatives include the following:



Compound	R1	R2	R3	Formula
270478	i-Bu	1-Naph	H	C ₅₀ H ₄₂ FN ₃ O ₆ S
270479	i-Bu	2-i-Pr-Ph	H	C ₄₉ H ₄₆ FN ₃ O ₆ S
270480	OEt	Ph	H	C ₄₄ H ₃₆ FN ₃ O ₇ S
270481	i-Bu	1-Naph	F	C ₅₀ H ₄₁ F ₂ N ₃ O ₆ S
270482	OMe	1-Naph	F	C ₄₇ H ₃₅ F ₂ N ₃ O ₇ S



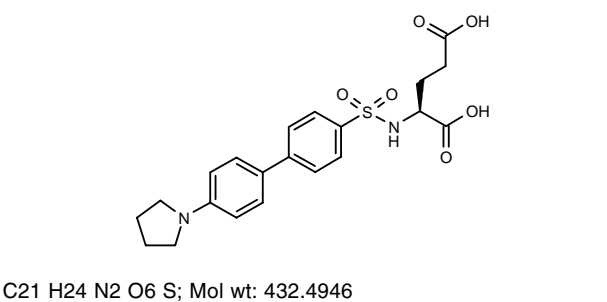
SOURCE – Shionogi.

REFERENCES

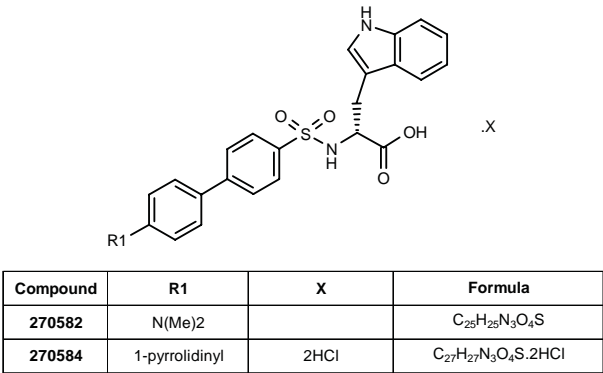
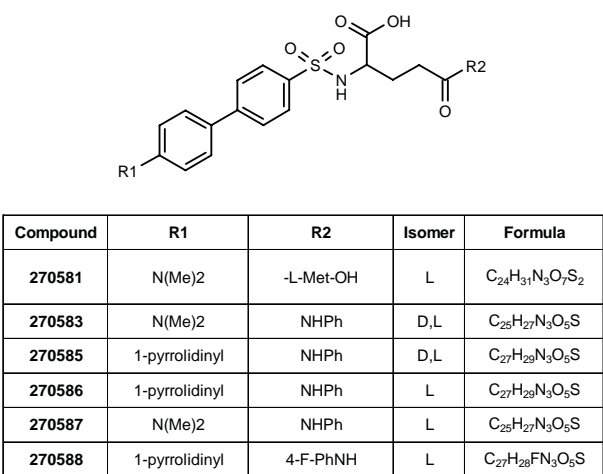
1. Seno, K. et al. (Shionogi & Co. Ltd.) *Pyrrolidine derivs. having phospholipase A2 inhibitory activity.* WO 9833797.

270580

N-[4'-(1-Pyrrolidinyl)biphenyl-4-ylsulfonyl]-L-glutamic acid



ACTION – Inhibitor of matrix metalloproteinases (MMPs) such as stromelysin (MMP-3; IC₅₀ = 4 nM) and neutrophil collagenase (MMP-8; IC₅₀ = 4 nM), potentially useful in the treatment of rheumatoid arthritis, osteoarthritis, spondylitis, periodontal disease, ulceration, restenosis, atherosclerosis, cancer, cachexia, anorexia and septic shock. Other compounds from this series of sulfonylaminocarboxylic acid derivatives include the following:



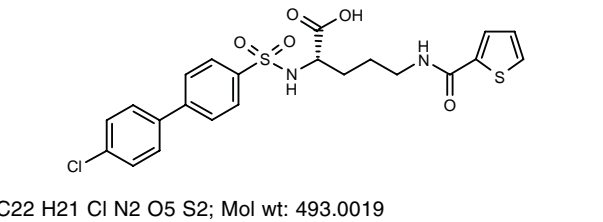
SOURCE – Hoechst Marion Roussel.

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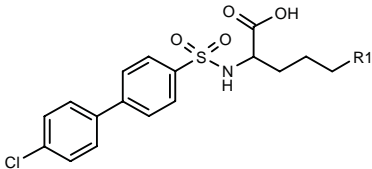
1. Thorwart, W. et al. (Hoechst AG) *Sulfonylaminocarboxylic acids.* EP 877018.

270589

N²-(4'-Chlorobiphenyl-4-ylsulfonyl)-N⁵-(2-thienyl-carbonyl)-L-ornithine



ACTION – Inhibitor of matrix metalloproteinases (MMPs) such as stromelysin (MMP-3; IC₅₀ = 3 nM) and neutrophil collagenase (MMP-8; IC₅₀ = 2 nM), potentially useful in the treatment of rheumatoid arthritis, osteoarthritis, spondylitis, periodontal disease, ulceration, restenosis, atherosclerosis, cancer, cachexia, anorexia and septic shock. Other compounds from this series of substituted diaminocarboxylic acids include the following:



Compound	R1	Isomer	Formula
270590	1-oxo-2-isindolinyl	R	C ₂₅ H ₂₃ ClN ₂ O ₅ S
270591	1-oxo-2-isindolinyl	S	C ₂₅ H ₂₃ ClN ₂ O ₅ S
270592	cyclopropyl-CONH	R	C ₂₁ H ₂₃ ClN ₂ O ₅ S
270593	2-Me-cyclopropyl-CONH	S	C ₂₂ H ₂₅ ClN ₂ O ₅ S
270594	(S)-NHCOCH2-CH2CH(Ph)CO2H	S	C ₂₈ H ₂₉ ClN ₂ O ₇ S
270595	3-Me-2-thienyl-CONH	S	C ₂₃ H ₂₃ ClN ₂ O ₅ S ₂
270596	3-oxo-2,3-dihydro-2-benzisothiazolyl	S	C ₂₄ H ₂₁ ClN ₂ O ₅ S ₂
270597	NHCOCH2CH2Ph	S	C ₂₆ H ₂₇ ClN ₂ O ₅ S
270598	5,7-dioxo-perhydro-imidazo[1,5-c]thiazol-6-yl	S	C ₂₂ H ₂₂ ClN ₃ O ₆ S ₂

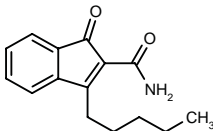
SOURCE – Hoechst Marion Roussel.

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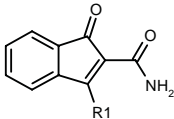
270662

1-Oxo-3-pentyl-1*H*-indene-2-carboxamide



C15 H17 N O2; Mol wt: 243.3043

ACTION – Inhibitor of leukocyte adhesion to endothelial cells, as demonstrated *in vitro* by inhibition of fMLP-stimulated adhesion of human neutrophils to keyhole-limpet hemocyanin (KLH) and to the ICAM-1-expressing endothelial cell line ECV304. Potentially useful for the treatment of rheumatoid arthritis, asthma, psoriasis, stroke, Alzheimer’s disease, respiratory distress syndrome, reperfusion injury, ischemia, vasculitis and inflammatory bowel disease. Other specifically claimed compounds from this series of indenone derivatives include the following:



Compound	R1	Formula
270663	i-Pr	C ₁₃ H ₁₃ NO ₂
270664	Ph	C ₁₆ H ₁₁ NO ₂
270665	3-Cl-Ph	C ₁₆ H ₁₀ ClNO ₂
270666	Et	C ₁₂ H ₁₁ NO ₂

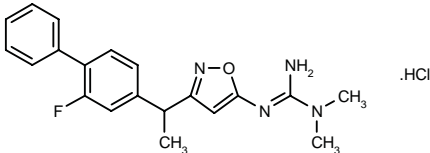
SOURCE – Lilly.

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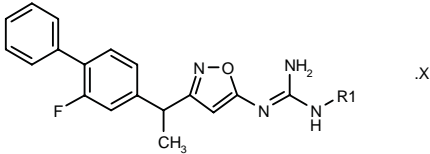
270684

*N*²-[3-[1-(2-Fluorobiphenyl-4-yl)ethyl]-5-isoxazolyl]-*N*¹,*N*¹-dimethylguanidine hydrochloride

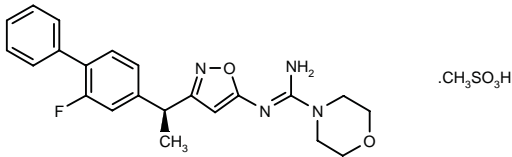


C20 H21 F N4 O . HCl; Mol wt: 388.8718

ACTION – Agent for the treatment of autoimmune and inflammatory disorders whose activity was tested in an adjuvant-induced arthritis model in rats, where it potently inhibited edema at 25 mg/kg p.o., being comparable to indomethacin at 0.5 mg/kg p.o. A representative compound from a series of isoxazole derivatives, wherein the following are also included:



Compound	R1	X	Formula
270685	H		C ₁₈ H ₁₇ FN ₄ O
270686	Me	HCl	C ₁₉ H ₁₉ FN ₄ O.HCl
270687	Et	HCl	C ₂₀ H ₂₁ FN ₄ O.HCl



270688: C22 H23 F N4 O2 .C H4 O3 S

Other exemplified compounds were effective in inhibiting a type III allergic reaction in mice or against experimental allergic encephalomyelitis in mice, the latter an animal model of multiple sclerosis.

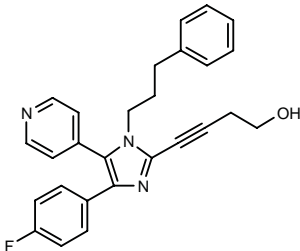
SOURCE – Sumitomo Pharmaceuticals.

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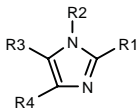
270783

4-[4-(4-Fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-3-butyne-1-ol



C27 H24 F N3 O; Mol wt: 425.5046

ACTION – An inhibitor of the production of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and IL-1 β that acts by inhibiting the activity of p38 MAP kinase (also known as CSBP kinase; IC₅₀ = 0.65 μ M). Compound was found to inhibit the lipopolysaccharide (LPS)-induced production of TNF- α both *in vitro* (IC₅₀ = 3.0 nM in peripheral blood mononuclear cells) and *in vivo* in mice and rats (49.6 and 91% inhibition, respectively, at 25 mg/kg p.o.). In the adjuvant-induced arthritis model in rats, it gave a 20% reduction in paw swelling at 50 mg/kg p.o. Potentially useful in the treatment of a broad range of conditions associated with the overproduction of cytokines such as rheumatoid arthritis, osteoarthritis, septic shock, inflammatory bowel disease, osteoporosis, neuropathic pain, AIDS, diabetes, periodontal disease, restenosis, psoriasis, allograft rejection, atherosclerosis, cachexia, Alzheimer's disease, stroke, ischemia and congestive heart failure. Within this series of substituted imidazoles, the following are also included:



Compound	R1	R2	R3	R4	Formula
270784	CH=CHCl	H	4-Pyr	4-F-Ph	C ₁₈ H ₁₁ ClFN ₃
270785	ethynylene-(CH ₂) ₃ CN	(CH ₂) ₃ Ph	4-Pyr	4-F-Ph	C ₂₉ H ₂₅ FN ₄
270786	ethynylene-(CH ₂) ₃ CN	H	4-F-Ph	4-Pyr	C ₂₀ H ₁₅ FN ₄
270787	ethynylene-Pr	H	4-F-Ph	4-Pyr	C ₁₉ H ₁₆ FN ₃

SOURCE – Ortho-McNeil.

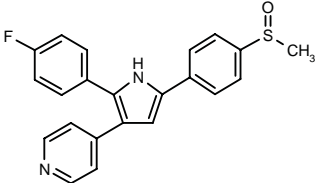
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L-167307

264017

4-[2-(4-Fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-1*H*-pyrrol-3-yl]pyridine



C22 H17 F N2 O S; Mol wt: 376.4533

ACTION – Potent inhibitor of p38 MAP (mitogen-activated protein) kinase (IC₅₀ = 5.1 nM) that is 8-fold more potent than the parent compound SB-203580 and shows high selectivity for subtypes p38 α and p38 β (IC₅₀ = 5 and 8.1 nM, respectively) and poor activity against other kinases. In functional studies, compound inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF- α) release from human monocytes with an IC₅₀ of 65 nM, showing similar potency to SB-203580. In the rat adjuvant-induced arthritis test, it reduced secondary paw swelling with an ID₅₀ of 7.4 mg/kg/day p.o., being more active than SB-203580 but less potent than indomethacin.

SOURCE – Merck & Co.

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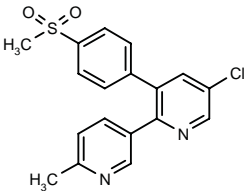
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L-791456*

261533

5-Chloro-3-[4-(methylsulfonyl)phenyl]-2-(6-methylpyridin-3-yl)pyridine



C18 H15 Cl N2 O2 S; Mol wt: 358.8475

ACTION – Orally active antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), with an IC_{50} of 81 nM for inhibition of PGE_2 production in CHO cells expressing human COX-2 and about 150-fold selectivity versus COX-1. *In vivo*, compound exhibited good antiinflammatory activity in the paw edema and pyresis models in rats, giving ED_{50} values of 0.6 and 0.5 mg/kg p.o., respectively, being more active than indomethacin. In models of pain and arthritis (carragenan-induced hyperalgesia in rats and adjuvant-induced arthritis in rats), it also showed good efficacy, displaying ID_{50} values of 0.3 mg/kg (indomethacin = 1.5 mg/kg) and 0.7 mg/kg/day b.i.d. (indomethacin = 0.2 mg/kg/day b.i.d.), respectively. No evidence of gastrointestinal toxicity was observed at a dose of 100 mg/kg b.i.d. for 10 days, whereas a single dose of indomethacin of 10 mg/kg was associated with significant toxicity.

SOURCE – Merck Frosst.

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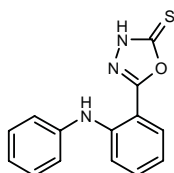
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*Identified compound **261533** Drug Data Report 1998, 020(05): 0432.

PD-057081

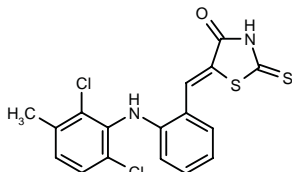
269781

5-[2-(Phenylamino)phenyl]-1,3,4-oxadiazole-2-thione



C14 H11 N3 O S; Mol wt: 269.3269

ACTION – Meclofenamic acid analogue with chondro-protective activity, as demonstrated against IL-1-induced human cartilage degradation (90% inhibition at 1 μ M). Compound inhibited IL-1-induced stromelysin production but had no effect on IL-1-induced production of IL-8, IL-6 and nitric oxide, suggesting that it acts by downregulating matrix metalloproteinase (MMP) expression. Another related compound is:



PD-137966 [191514]: C17 H12 Cl2 N2 O S2

SOURCE – Warner-Lambert.

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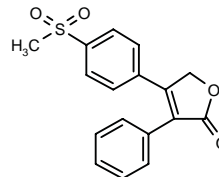
ROFECOXIB*

221147

4-[4-(Methylsulfonyl)phenyl]-3-phenylfuran-2(5H)-one

MK-966

Vioxx™



C17 H14 O4 S; Mol wt: 314.3596

ACTION – Antiinflammatory agent, a highly selective inhibitor of cyclooxygenase type 2 (COX-2), with > 1000-fold selectivity relative to COX-1 *in vitro*. It is currently undergoing FDA review for the once-daily treatment of osteoarthritis and pain.

SOURCE – Merck & Co.

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2. Desmond, R. et al. (Merck & Co., Inc.) *Process for making phenyl heterocycles useful as COX-2 inhibitors*. WO 9608482.

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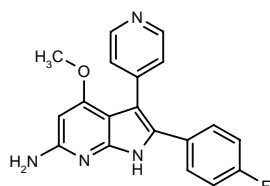
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*Identified compound **221147** (see **218596**) Drug Data Report 1995, 017(05): 0470.

RWJ-68354

269887

6-Amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridine



C19 H15 F N4 O; Mol wt: 334.3525

ACTION – Potent and selective inhibitor of cellular p38 MAP (mitogen-activated protein) kinase ($IC_{50} = 9$ nM) shown to reduce lipopolysaccharide (LPS)-stimulated tumor necrosis factor (TNF- α) and IL-1 β production in human peripheral blood mononuclear cells ($IC_{50} = 6.3$ and 26 nM, respectively). *In vivo*, compound at a dose of 25 mg/kg p.o. completely inhibited the LPS-stimulated production of TNF- α in both mice and rats, and a dose of 50 mg/kg/day p.o. reduced hind paw swelling by 50% in rats with adjuvant-induced arthritis. It is considered a promising candidate for clinical evaluation.

SOURCE – R.W. Johnson.

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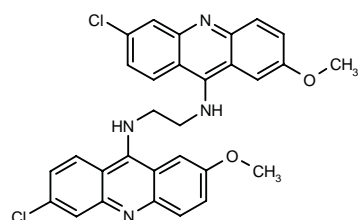
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SB-262105

269722

N,N'-Bis(6-chloro-2-methoxyacridin-9-yl)ethanediamine



C30 H24 Cl2 N4 O2; Mol wt: 543.4516

ACTION – Selective, small-molecule chemokine CCR5 antagonist proven to inhibit both RANTES- and MIP-1 β -induced T-cell migration. Potentially useful for the treatment of chronic inflammatory disorders.

SOURCE – SmithKline Beecham.

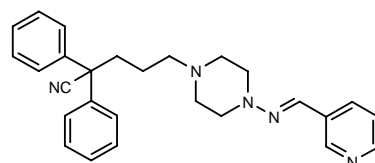
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SC-26196

270131

2,2-Diphenyl-5-[4-(3-pyridylmethyleneamino)piperazin-1-yl]pentanenitrile



C27 H29 N5; Mol wt: 423.5611

ACTION – Potent and selective Δ^6 fatty acid desaturase inhibitor, as demonstrated *in vitro* ($IC_{50} = 0.2$ μ M in rat liver microsomes; $IC_{50} > 200$ μ M against Δ^5 and Δ^9 fatty acid desaturases) and *in vivo* by inhibition of the conversion of [14 C]-linoleic acid to [14 C]- γ -linolenic acid + [14 C]-dihomo- γ -linolenic acid + [14 C]-arachidonic acid in mice (at least 95% at a dose of 100 mg/kg i.p. or i.g.). Antiinflammatory activity was observed in mice in the carrageenan-induced paw edema test, with 50% inhibition of edema at 100 mg/kg i.p. b.i.d. for 9 days.

SOURCE – Searle.

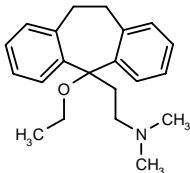
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SCH-23863*

227195

N-[2-(5-Ethoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethyl]-N,N-dimethylamine



C21 H27 N O; Mol wt: 309.4503

ACTION – Inhibitor of the production of inflammatory cytokines that also upregulates the production of the antiinflammatory cytokine IL-10. In a mouse model of lethal endotoxemia, compound administered orally produced a dose-related inhibition of lipopolysaccharide (LPS)-stimulated serum TNF-α, interferon gamma, IL-1α and IL-6, with a maximum inhibitory effect (approx. 90%) at 50 mg/kg. At the same dose compound produced a 30-fold increase in the LPS-stimulated serum levels of IL-10. It also exhibited good antiinflammatory activity in several models of chronic inflammatory diseases.

SOURCE – Schering-Plough.

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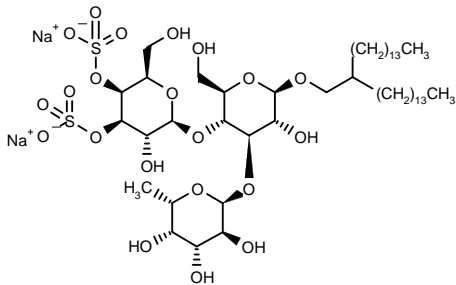
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*Identified compound 227195 Drug Data Report 1996, 018(01): 0049.

IMMUNOMODULATING AGENTS

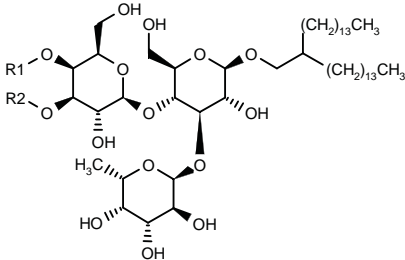
265911

2-Tetradecylhexadecyl 3-O-(6-deoxy-α-L-galactopyranosyl)-4-O-(3,4-di-O-sulfo-β-D-galactopyranosyl)-β-D-glucopyranoside disodium salt



C48 H90 Na2 O21 S2; Mol wt: 1113.33

ACTION – Immunosuppressant, an inhibitor of the expression of the adhesion molecule B7-2, as demonstrated in murine peritoneal exudate cells stimulated by lipopolysaccharide (64.6 ± 2.2% inhibition at 100 μM). Other representative compounds within this series of glycolipid derivatives include the following:



Compound	R1	R2	Formula
266654	SO3 ⁻ Na ⁺	H	C ₄₈ H ₉₁ NaO ₁₈ S
266655	H	SO3 ⁻ Na ⁺	C ₄₈ H ₉₁ NaO ₁₈ S

SOURCE – Kanebo.

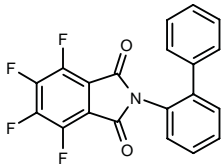
REFERENCES

1. Yoshida, M. et al. (Kanebo, Ltd.) *Glycolipid derivs., immunosuppressant containing them and intermediates for their production.* JP 98152498.

269344

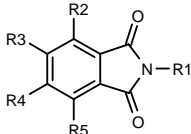
N-(2-Biphenyl)-3,4,5,6-tetrafluorophthalimide

2-(2-Biphenyl)-4,5,6,7-tetrafluoroisindoline-1,3-dione



C20 H9 F4 N O2; Mol wt: 371.2881

ACTION – Immunomodulating agent with tumor necrosis factor-α (TNF-α) production-regulating activity, potentially useful for the treatment of disorders where it is necessary to modulate TNF-α production, as an immunomodulator, antitumor, antiinflammatory and antidiabetic agent and for inhibiting neovascularization. Within this series of phthalimido derivatives, the following are also included:



Compound	R1	R2=R2=R3=R4=R5	Formula
269345	2-Ph-Ph	H	C ₂₀ H ₁₃ NO ₂
269346	3,5-(Me)2-4-isoxazoly-CH2	F	C ₁₄ H ₈ F ₄ N ₂ O ₃
269347	1-indanyl	F	C ₁₇ H ₉ F ₄ NO ₂

SOURCE – Ishihara Sangyo.

REFERENCES

1. Hashimoto, Y. (Ishihara Sangyo Kaisha, Ltd.) *Phthalimido derivs. or their salts, their preparation method and medicinal compsns. containing them.* JP 9821285.

SOURCE – Searle.

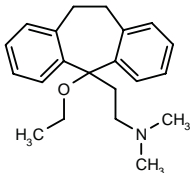
REFERENCES

1. Obukowicz, M.G. et al. *Novel, selective Δ⁶ or Δ⁵ fatty acid desaturase inhibitors as antiinflammatory agents in mice.* J Pharmacol Exp Ther 1998, 287(1): 157.

SCH-23863*

227195

N-[2-(5-Ethoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethyl]-N,N-dimethylamine



C21 H27 N O; Mol wt: 309.4503

ACTION – Inhibitor of the production of inflammatory cytokines that also upregulates the production of the antiinflammatory cytokine IL-10. In a mouse model of lethal endotoxemia, compound administered orally produced a dose-related inhibition of lipopolysaccharide (LPS)-stimulated serum TNF-α, interferon gamma, IL-1α and IL-6, with a maximum inhibitory effect (approx. 90%) at 50 mg/kg. At the same dose compound produced a 30-fold increase in the LPS-stimulated serum levels of IL-10. It also exhibited good antiinflammatory activity in several models of chronic inflammatory diseases.

SOURCE – Schering-Plough.

REFERENCES

1. Ting, P.C. et al. (Schering Corp.) *Tricyclic derivs., pharmaceutical compsns. containing them.* EP 733035, JP 97500656, US 5538986, WO 9515939.

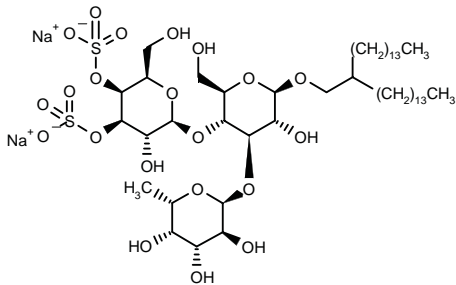
2. Terminelli, C. et al. *Sch 23863, is an inhibitor of inflammatory cytokines and a potent stimulator of antiinflammatory IL-10 in the Corynebacterium parvum mouse model of lethal endotoxemia.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst W30.

*Identified compound 227195 Drug Data Report 1996, 018(01): 0049.

IMMUNOMODULATING AGENTS

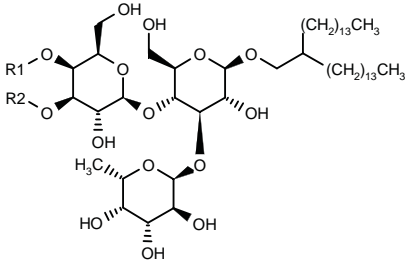
265911

2-Tetradecylhexadecyl 3-O-(6-deoxy-α-L-galactopyranosyl)-4-O-(3,4-di-O-sulfo-β-D-galactopyranosyl)-β-D-glucopyranoside disodium salt



C48 H90 Na2 O21 S2; Mol wt: 1113.33

ACTION – Immunosuppressant, an inhibitor of the expression of the adhesion molecule B7-2, as demonstrated in murine peritoneal exudate cells stimulated by lipopolysaccharide (64.6 ± 2.2% inhibition at 100 μM). Other representative compounds within this series of glycolipid derivatives include the following:



Compound	R1	R2	Formula
266654	SO3 ⁻ Na ⁺	H	C ₄₈ H ₉₁ NaO ₁₈ S
266655	H	SO3 ⁻ Na ⁺	C ₄₈ H ₉₁ NaO ₁₈ S

SOURCE – Kanebo.

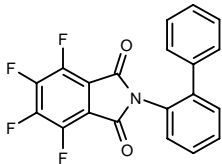
REFERENCES

1. Yoshida, M. et al. (Kanebo, Ltd.) *Glycolipid derivs., immunosuppressant containing them and intermediates for their production.* JP 98152498.

269344

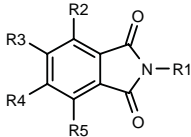
N-(2-Biphenyl)-3,4,5,6-tetrafluorophthalimide

2-(2-Biphenyl)-4,5,6,7-tetrafluoroisindoline-1,3-dione



C20 H9 F4 N O2; Mol wt: 371.2881

ACTION – Immunomodulating agent with tumor necrosis factor-α (TNF-α) production-regulating activity, potentially useful for the treatment of disorders where it is necessary to modulate TNF-α production, as an immunomodulator, antitumor, antiinflammatory and antidiabetic agent and for inhibiting neovascularization. Within this series of phthalimido derivatives, the following are also included:



Compound	R1	R2=R2=R3=R4=R5	Formula
269345	2-Ph-Ph	H	C ₂₀ H ₁₃ NO ₂
269346	3,5-(Me)2-4-isoxazoly-CH2	F	C ₁₄ H ₈ F ₄ N ₂ O ₃
269347	1-indanyl	F	C ₁₇ H ₉ F ₄ NO ₂

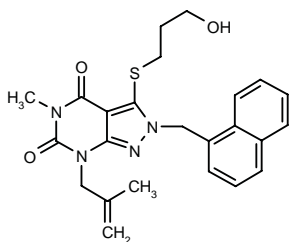
SOURCE – Ishihara Sangyo.

REFERENCES

1. Hashimoto, Y. (Ishihara Sangyo Kaisha, Ltd.) *Phthalimido derivs. or their salts, their preparation method and medicinal compsns. containing them.* JP 98231285.

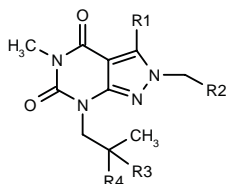
270283

3-(3-Hydroxypropylsulfanyl)-5-methyl-7-(2-methyl-2-propenyl)-2-(1-naphthylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidine-4,6-dione



C₂₄ H₂₆ N₄ O₃ S; Mol wt: 450.5604

ACTION – Agent for the treatment of autoimmune, inflammatory, proliferative and hyperproliferative disorders; it is reported to have an IA_{50} value below 1 μ M in a human mixed lymphocyte reaction. Other specifically claimed pyrazolo[3,4-d]pyrimidinedione derivatives include the following:



Compound	R1	R2	R3	R4	Formula
270284	2-Pyr-S	1-Naph	-CH2-		C ₂₆ H ₂₃ N ₅ O ₂ S
270285	SCH ₂ CH ₂ OH	1-Naph	-CH2-		C ₂₃ H ₂₄ N ₄ O ₃ S
270286	(CH ₂) ₄ OH	1-Naph	Me	H	C ₂₅ H ₃₀ N ₄ O ₃
270287	SPr	1-Naph	Me	H	C ₂₄ H ₂₆ N ₄ O ₂ S
270288	S(CH ₂) ₃ OH	1-Naph	Me	H	C ₂₄ H ₂₆ N ₄ O ₃ S
270289	S(CH ₂) ₃ -CO ₂ Me	1-Naph	Me	H	C ₂₆ H ₃₀ N ₄ O ₄ S
270290	S(CH ₂) ₃ -CO ₂ H	1-Naph	Me	H	C ₂₅ H ₂₆ N ₄ O ₄ S
270291	S(CH ₂) ₃ OH	2-(PhSO ₂ CH ₂)-Ph	Me	H	C ₂₇ H ₃₂ N ₄ O ₅ S ₂
270292	S(CH ₂) ₃ OH	6-Cl-1,3-benzodioxol-5-yl	Me	H	C ₂₁ H ₂₅ ClN ₄ O ₅ S
270293	S(CH ₂) ₃ OH	2-F-3-Cl-Ph	Me	H	C ₂₀ H ₂₄ ClF ₂ N ₄ O ₃ S
270294	S(CH ₂) ₃ OH	2-quinolinyl	Me	H	C ₂₃ H ₂₇ N ₅ O ₃ S

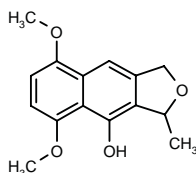
SOURCE – Astra.

REFERENCES

1. Cheshire, D. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds.* WO 9846606.

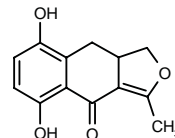
270467

5,8-Dimethoxy-3-methyl-1,3-dihydronaphtho[2,3-c]furan-4-ol



C₁₅ H₁₆ O₄; Mol wt: 260.2874

ACTION – Immunosuppressive and antipruritic agent, a derivative of MS-444 found to inhibit T-cell proliferation with comparable potency to the parent compound. Additionally, it inhibited compound 48/80-induced itching at 30 and 100 mg/kg i.p. in mice (39 and 86% inhibition, respectively). Another related compound is:



270468: C₁₃ H₁₂ O₄

SOURCE – Kyowa Hakko.

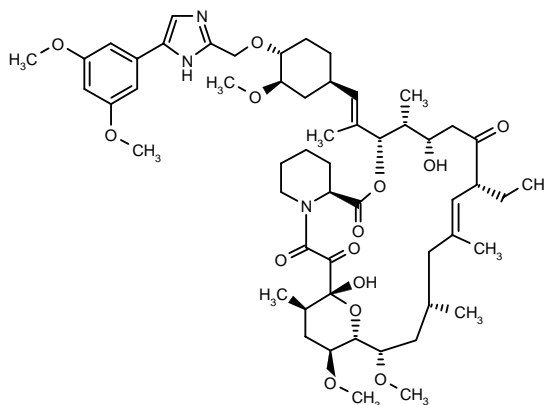
REFERENCES

1. Tatsuta, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *MS-444 derivs.* WO 9832750.

L-733725

267936

[3S-[3^{*}R[E(1S^{*},3S^{*}4S^{*})],4S^{*},5R^{*},8S^{*},9E,12R^{*},14R^{*},15S^{*},16R^{*},18S^{*},19S^{*},26aR^{*}]]-3-[2-[4-[4-(3,5-Dimethoxyphenyl)-1H-imidazol-2-ylmethoxy]-3-methoxycyclohexyl]-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21-(4H,23H)-tetraone



C₅₅ H₈₁ N₃ O₁₄; Mol wt: 1008.252

ACTION – Immunosuppressant with an improved therapeutic index compared to the parent compounds ascomycin and tacrolimus (FK-506). *In vitro* in murine spleen T-cells activated with PMA and ionomycin, compound was at least as active as FK-506 (IC_{50} = 0.20 nM vs. 0.29 nM) and 3 times more potent than ascomycin. *Ex vivo* in mice, compound showed an immunosuppressive ED_{50} of 0.33 ± 0.07 and 4.4 ± 0.4 mg/kg i.v. and p.o., respectively; however, it was less neurotoxic in the mouse hypothermia model than FK-506 after i.v. administration (ED_{50} = 18.6 ± 5.6 and 3.5 ± 0.6 mg/kg, respectively), giving a therapeutic index about 4-fold higher (56 vs. 15). Considered a promising candidate for further evaluation.

SOURCE – Merck & Co.

REFERENCES

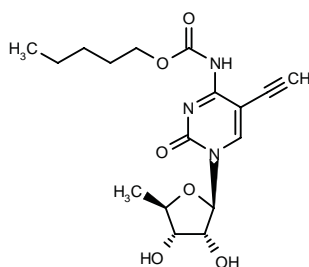
1. Goulet, M. et al. (Merck & Co., Inc.) *Imidazolidyl macrolides having immunosuppressive activity*. EP 536896, JP 94510303, US 5247076, WO 9305059.
2. Goulet, M. et al. (Merck & Co., Inc.) *Imidazolidyl macrolides having immunosuppressive activity*. US 5344925.
3. Mathre, D.J. et al. (Merck & Co., Inc.) *Process for the preparation of imidazolidyl macrolide immunosuppressants*. US 5777105, WO 9708182.
4. Goulet, M.T. et al. *C32-O-Imidazol-2-yl-methyl ether derivatives of the immunosuppressant ascomycin with improved therapeutic potential*. Bioorg Med Chem Lett 1998, 8(16): 2253.

ONCOLYTIC DRUGS

INHIBITORS OF THE DEGRADATION OF ANTICANCER AGENTS

270622

5'-Deoxy-5-ethynyl-*N*⁴-(pentyloxycarbonyl)cytidine



C17 H23 N3 O6; Mol wt: 365.3837

ACTION – Dihydropyrimidine dehydrogenase (DPD) inhibitor for use in combination with 5-fluorouracil (5-FU) and other fluoropyrimidines, shown to selectively inhibit DPD in tumor tissue in contrast to known DPD inhibitors such as 5-ethynyluracil, thereby resulting in selective delivery of 5-FU to tumor tissues, whereby the efficacy of the latter is enhanced without increasing its systemic toxicity. It was also shown to significantly improve the antitumor activity of capecitabine in nude mice bearing human prostate cancer PC-3 xenografts.

SOURCE – Roche.

REFERENCES

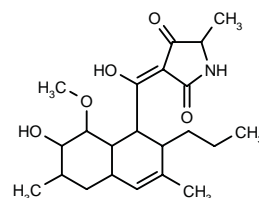
1. Hattori, K. et al. (F. Hoffmann-La Roche AG) *5'-Deoxy-cytidine derivs*. EP 882734, JP 98330395.

ANTIBIOTICS AND ALKALOIDS

TEL-0010

269843

3-[1-Hydroxy-1-(7-hydroxy-8-methoxy-3,6-dimethyl-2-propyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-methylene]-5-methylpyrrolidine-2,4-dione



C22 H33 N O5; Mol wt: 391.5047

ACTION – Antineoplastic agent isolated from the microorganism *Streptomyces* sp. TA-0358 (FERM BP-6268), with *in vitro* cytotoxic activity against human leukemia HL-60 cells (IC₅₀ = 10.0 µg/ml) and against human nasopharyngeal cancer KB cells (IC₅₀ = 5.9 µg/ml); the corresponding IC₅₀ values for doxorubicin were 0.016 and 0.046 µg/ml.

SOURCE – Taisho.

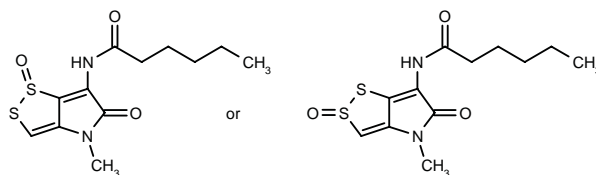
REFERENCES

1. Sugawara, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Tetramic acid cpds*. JP 98330360, WO 9843955.

XENOMIN 1

269865

N-(4-Methyl-1(or 2)-oxido-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrol-6-yl)hexanamide



C12 H16 N2 O3 S2; Mol wt: 300.4014

ACTION – Antineoplastic antibiotic produced by culturing the microorganism *Xenorhabdus bovienii* strain A21 (ATCC5S743), active *in vitro* against Gram-positive bacteria including resistant strains such as *Staphylococcus aureus* 0012 (methicillin-resistant; MIC = 10 µg/ml). Cytotoxic activity was assessed *in vitro* in several human cancer cell lines including colon cancer HT-29 (IC₅₀ = 0.14 µg/ml), breast cancer MCF-7 (IC₅₀ = 1.37 µg/ml) and cervical cancer HeLa cells (IC₅₀ = 0.24 µg/ml). Another compound isolated from this microorganism is:

SOURCE – Merck & Co.

REFERENCES

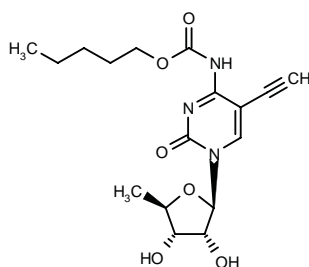
1. Goulet, M. et al. (Merck & Co., Inc.) *Imidazolidyl macrolides having immunosuppressive activity*. EP 536896, JP 94510303, US 5247076, WO 9305059.
2. Goulet, M. et al. (Merck & Co., Inc.) *Imidazolidyl macrolides having immunosuppressive activity*. US 5344925.
3. Mathre, D.J. et al. (Merck & Co., Inc.) *Process for the preparation of imidazolidyl macrolide immunosuppressants*. US 5777105, WO 9708182.
4. Goulet, M.T. et al. *C32-O-Imidazol-2-yl-methyl ether derivatives of the immunosuppressant ascomycin with improved therapeutic potential*. Bioorg Med Chem Lett 1998, 8(16): 2253.

ONCOLYTIC DRUGS

INHIBITORS OF THE DEGRADATION OF ANTICANCER AGENTS

270622

5'-Deoxy-5-ethynyl-*N*⁴-(pentyloxycarbonyl)cytidine



C17 H23 N3 O6; Mol wt: 365.3837

ACTION – Dihydropyrimidine dehydrogenase (DPD) inhibitor for use in combination with 5-fluorouracil (5-FU) and other fluoropyrimidines, shown to selectively inhibit DPD in tumor tissue in contrast to known DPD inhibitors such as 5-ethynyluracil, thereby resulting in selective delivery of 5-FU to tumor tissues, whereby the efficacy of the latter is enhanced without increasing its systemic toxicity. It was also shown to significantly improve the antitumor activity of capecitabine in nude mice bearing human prostate cancer PC-3 xenografts.

SOURCE – Roche.

REFERENCES

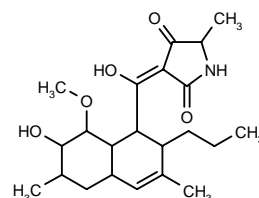
1. Hattori, K. et al. (F. Hoffmann-La Roche AG) *5'-Deoxy-cytidine derivs*. EP 882734, JP 98330395.

ANTIBIOTICS AND ALKALOIDS

TEL-0010

269843

3-[1-Hydroxy-1-(7-hydroxy-8-methoxy-3,6-dimethyl-2-propyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-methylene]-5-methylpyrrolidine-2,4-dione



C22 H33 N O5; Mol wt: 391.5047

ACTION – Antineoplastic agent isolated from the microorganism *Streptomyces* sp. TA-0358 (FERM BP-6268), with *in vitro* cytotoxic activity against human leukemia HL-60 cells (IC_{50} = 10.0 μ g/ml) and against human nasopharyngeal cancer KB cells (IC_{50} = 5.9 μ g/ml); the corresponding IC_{50} values for doxorubicin were 0.016 and 0.046 μ g/ml.

SOURCE – Taisho.

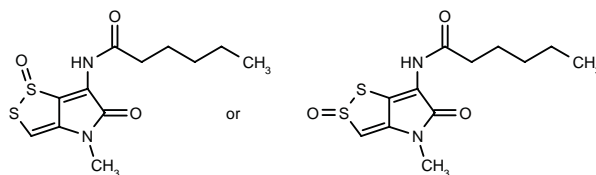
REFERENCES

1. Sugawara, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Tetramic acid cpds*. JP 98330360, WO 9843955.

XENOMIN 1

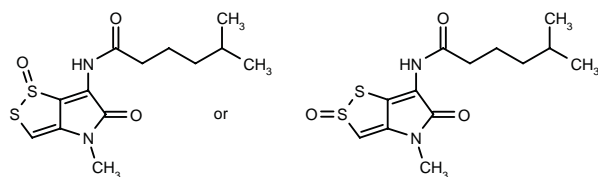
269865

N-(4-Methyl-1(or 2)-oxido-5-oxo-4,5-dihydro-1,2-dithio-[4,3-*b*]pyrrol-6-yl)hexanamide



C12 H16 N2 O3 S2; Mol wt: 300.4014

ACTION – Antineoplastic antibiotic produced by culturing the microorganism *Xenorhabdus bovienii* strain A21 (ATCC5S743), active *in vitro* against Gram-positive bacteria including resistant strains such as *Staphylococcus aureus* 0012 (methicillin-resistant; MIC = 10 μ g/ml). Cytotoxic activity was assessed *in vitro* in several human cancer cell lines including colon cancer HT-29 (IC_{50} = 0.14 μ g/ml), breast cancer MCF-7 (IC_{50} = 1.37 μ g/ml) and cervical cancer HeLa cells (IC_{50} = 0.24 μ g/ml). Another compound isolated from this microorganism is:



Xenomin 2 [269866]: C₁₃ H₁₈ N₂ O₃ S₄

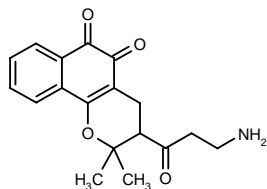
REFERENCES

1. Webster, J.M. et al. *Xenomins novel heterocyclic cpds. with antimicrobial and antineoplastic properties.* US 5827872.

DNA-INTERCALATING DRUGS

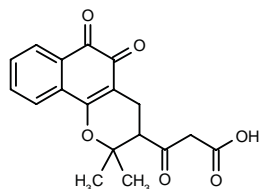
269505

3-(β -Alanyl)-2,2-dimethyl-3,4,5,6-tetrahydro-2*H*-naphtho-[1,2-*b*]pyran-5,6-dione



C₁₈ H₁₉ N O₄; Mol wt: 313.3511

ACTION – Antineoplastic agent that acts by inhibiting topoisomerases I and II. Another specifically claimed compound from this series of β -lapachone derivatives is:



269506: C₁₈ H₁₆ O₆

SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

REFERENCES

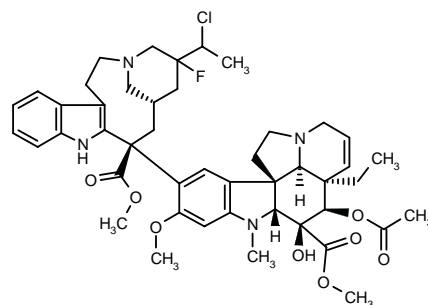
1. Frydman, B.J. et al. (Wisconsin Alumni Research Foundation) *Ortho-quinone derivs. novel synthesis therefor and their use in the inhibition of neoplastic cell growth.* US 5824700.

ANTIMITOTIC DRUGS

269954

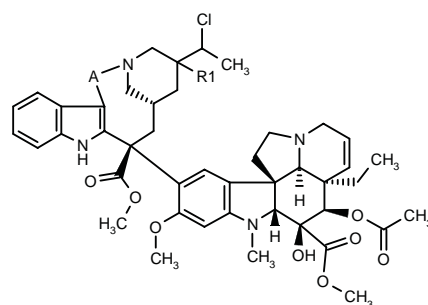
20'-Chloro-4'-deoxy-4'-fluorovinblastine

(10*bR*)-4(*R*)-Acetoxy-9-[5-(1-chloroethyl)-5-fluoro-9(*S*)-(methoxycarbonyl)-1,2,3,4,5,6,7(*S*),8,9,10-decahydro-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-3a(*R*)-ethyl-5(*S*)-hydroxy-8-methoxy-6-methyl-3a,4,5,5a(*R*),6,11,12,13a(*R*)-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylic acid methyl ester



C₄₆ H₅₆ Cl F N₄ O₈; Mol wt: 847.4194

ACTION – Antimitotic alkaloid, a derivative of vinblastine found to inhibit tubulin polymerization in a microtubule assay (IC₅₀ = 1.54 μ M vs. 1.70 μ M for vinorelbine). Within this series of halogenated derivatives of vinca alkaloids, the following are also specifically claimed:



Compound	R1	A	Formula
269955	H	-(CH ₂) ₂ -	C ₄₆ H ₅₇ ClN ₄ O ₈
269956	H	-CH ₂ -	C ₄₅ H ₅₅ ClN ₄ O ₈
269957	F	-CH ₂ -	C ₄₅ H ₅₄ ClFN ₄ O ₈

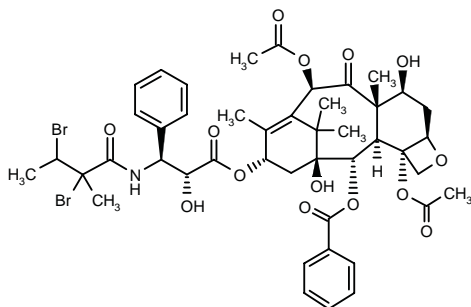
SOURCE – Pierre Fabre.

REFERENCES

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270544

[2a*R*]-[2a α ,4 β ,4a β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12a α ,12b α]]-6,12b-Diacetoxy-9-[3-(2,3-dibromobutyramino-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-4,11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz-[1,2-*b*]oxet-5-one



C45 H53 Br2 N O14; Mol wt: 991.7147

ACTION – Antineoplastic agent, a derivative of cephalomannine that exhibits potent paclitaxel-like *in vitro* cytotoxicity in the NCI 60 human tumor cell line panel, particularly against non-small cell lung cancer NCI-H522, colon cancer COLO 205, CNS cancer SNB-75 and breast cancer HS 578T cell lines.

SOURCE – Xechem.

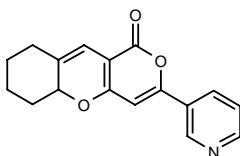
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H10¹⁻⁴

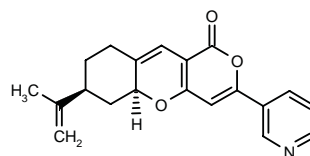
269096

3-(3-Pyridinyl)-1,5a,6,7,8,9-hexahydropyrano[4,3-*b*]-chromen-1-one

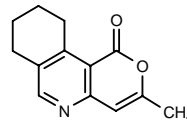


C17 H15 N O3; Mol wt: 281.3095

ACTION – Antineoplastic agent, a microtubule-destabilizing agent; it was less potent than vincristine against tubulin polymerization ($IC_{50} = 1.5 \mu M$ vs. $0.15 \mu M$) and murine mammary sarcoma EMT-6 tumor cell proliferation ($IC_{50} = 1.5 \mu M$ vs. $5 nM$), but it inhibited DNA synthesis ($IC_{50} = 10 \mu M$) more effectively than other microtubule-disrupting agents. Compound increased the percentage of mitotic cells, arresting the cell cycle in the M phase like vincristine. Other compounds from this series of tricyclic pyrone analogues include the following:



H14 [269097]¹⁻³: C20 H19 N O3



H16 [269098]³: C13 H13 N O2

SOURCE – Kansas State University, Manhattan, KS (US).

REFERENCES

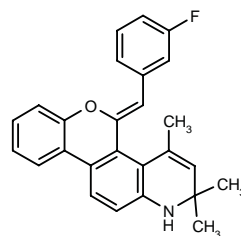
1. Hua, D.H. et al. *A one-pot condensation of pyrones and enals. Synthesis of 1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyrans*. J Org Chem 1997, 62(20): 6888.
2. Newell, S.W. et al. *Tricyclic pyrone analogs: A new class of microtubule-disrupting anticancer drugs effective against murine leukemia cells in vitro*. Int J Oncol 1998, 12(2): 433.
3. Perchellet, E.M. et al. *Antitumor activity of tricyclic pyrone analogs, a new synthetic class of microtubule de-stabilizing agents, in the murine EMT-6 mammary tumor cell line in vitro*. Anti-Cancer Drugs 1998, 9(6): 565.
4. Perchellet, J.-P. et al. *Antitumor activity of novel tricyclic pyrone analogs in murine leukemia cells in vitro*. Anticancer Res 1997, 17(4A): 2427.

HORMONAL AGENTS

LG-120744

269895

(*Z*)-5-(3-Fluorobenzylidene)-2,2,4-trimethyl-2,5-dihydro-1*H*-[1]benzopyrano[3,4-*f*]quinoline



C26 H22 F N O; Mol wt: 383.4638

Yellow solid, m.p. 66-7 °C.

ACTION – Nonsteroidal human progesterone (PR) receptor agonist that displays high affinity for human PR subtype A (PR-A) receptors ($K_i = 0.83 nM$) and good selectivity relative to human androgen ($K_i = 798 nM$) and human glucocorticoid receptors ($K_i = 180 nM$). Compound exhibited good agonist activity in a cotransfection assay in CV-1 cells ($IC_{50} = 7.6 nM$; 132% of progesterone activity). In ovariectomized rats, compound inhibited the estrogen-stimulated increase in uterine wet weight and it stimulated mammary alveolar bud formation in the dose range of 0.3-3 mg/rat p.o. for 3 days, with similar potency to medroxyprogesterone acetate. Potentially useful for the treatment of dysmenorrhea, breast cancer, as hormone replacement therapy or for oral contraception.

SOURCE – Ligand.

REFERENCES

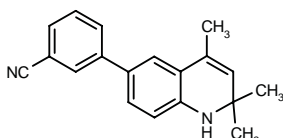
1. Jones, T.K. et al. (Ligand Pharmaceuticals, Inc.) *Steroid receptor modulator cpds. and methods*. EP 800519, JP 98510840, US 5688808, US 5688810, US 5693646, US 5693647, US 5696127, US 5696130, US 5696133, WO 9619458.

2. Tegley, C.M. et al. *5-Benzylidene 1,2-dihydrochromeno[3,4-f]quinolines, a novel class of nonsteroidal human progesterone receptor agonists*. J Med Chem 1998, 41(22): 4354.

LG-120753

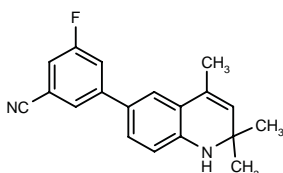
268113

3-(2,2,4-Trimethyl-1,2-dihydro-6-quinoliny)benzonitrile



C19 H18 N2; Mol wt: 274.3652

ACTION – Nonsteroidal human progesterone receptor (hPR) antagonist, as demonstrated in a cotransfection assay using the hPR isoform B and CV-1 cells ($IC_{50} = 38 \pm 6$ nM) and in a binding assay using baculovirus-expressed hPR isoform A ($K_i = 19$ nM), with potency comparable to the steroidal hPR antagonist onapristone and low crossreactivity with other steroid receptors (human androgen, estrogen, mineralocorticoid and glucocorticoid receptors). *In vivo*, compound at doses of 0.1-5 mg/kg p.o. blocked implantation in mated female mice in a dose-dependent manner; its antifertility effects were completely reversed by coadministration of the progestin R-5020, indicating that its effects are due to antiprogesterone activity rather than toxicity. Potentially useful as a lead compound for the development of nonsteroidal antiprogesterone agents for the treatment of gynecological disorders, particularly cancer. Another related compound is:



LG-120830 [268114]: C19 H17 F N2

SOURCE – Ligand.

REFERENCES

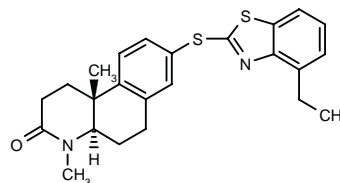
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LY-320236*

235179

(4*aR*,10*bR*)-8-(4-Ethylbenzothiazol-2-ylsulfanyl)-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



C24 H26 N2 O S2; Mol wt: 422.6144

ACTION – Potent and competitive inhibitor of human type 1 5α -reductase ($K_i = 28.7 \pm 1.87$ nM against enzyme from human scalp skin) and noncompetitive inhibitor of human type 2 enzyme ($K_i = 10.6 \pm 4.5$ nM against enzyme from prostatic homogenates) with potential in the treatment of prostate cancer. It significantly antagonized testosterone-stimulated human prostatic adenocarcinoma LNCaP cell proliferation at a concentration of 0.3 μ M, with complete inhibition at a concentration of 3 μ M; it also significantly inhibited PSA (prostate-specific antigen) secretion stimulated by testosterone at concentrations of 1 μ M and above. Compound was also effective in an LNCaP xenograft model.

SOURCE – Lilly.

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4. Brennan, J. et al. (Eli Lilly and Company) *Synthesis of benzo[f]quinolinones*. WO 9818757.

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6. Brennan, J. et al. *Novel synthesis of aryl sulfides facilitates production of the 5 α -reductase inhibitor LY320236*. 216th ACS Natl Meet (Aug 23-28, Boston) 1998, Abst ORGN 152.

7. McNulty, A.M. et al. *Kinetic analysis of LY320236: Competitive inhibitor of human type I and non-competitive inhibitor of human type II 5 α -reductase*. Proc Amer Assoc Cancer Res 1997, 38: Abst 3864.

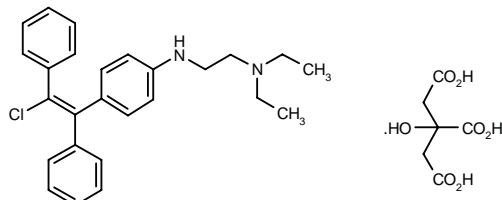
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9. Udodong, U.E. et al. *A new synthetic route that defines a manufacturing process of LY320236, a type I/II 5 α -reductase inhibitor*. 216th ACS Natl Meet (Aug 23-28, Boston) 1998, Abst ORGN 153.

*Identified compound **235179** Drug Data Report 1996, 018(06): 0534.

MDL-101986***210527***(E)*-*N'*-[4-(2-Chloro-1,2-diphenylvinyl)phenyl]-*N,N*-diethyl-1,2-ethanediamine citrate (1:1)

MDL-10222F (as undefined isomer)



C26 H29 Cl N2 . C6 H8 O7; Mol wt: 597.1043

ACTION – Nonsteroidal estrogen receptor modulator, a clomiphene analogue with antiproliferative activity against human breast cancer MCF-7 (estrogen receptor-positive, tamoxifen-susceptible), LY2 (estrogen receptor-positive, tamoxifen-resistant) and MDA-MB-231 (estrogen receptor-negative, tamoxifen-resistant) cells (IC_{50} = 0.7, 4.0 and 6.2 μ M, respectively). In nude mice bearing MCF-7 tumor xenografts, compound was over 10-fold more active than clomiphene, exhibiting an ED_{50} < 0.02 mg/mouse/day for 6 weeks p.o. Moreover, in aged, ovariectomized, osteoporotic rats, it increased bone mineral mass and restored proximal tibial bone strength at oral doses of 0.03-1.0 mg/kg/day for 16 weeks. Potentially useful for the treatment of estrogen-dependent breast cancer and in the prevention of postmenopausal bone loss.

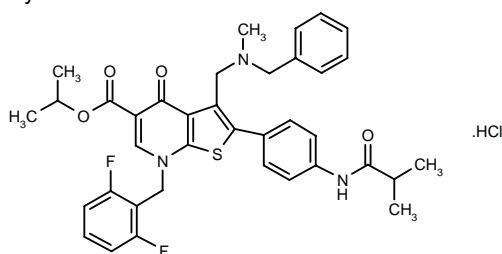
SOURCE – Hoechst Marion Roussel.**REFERENCES**

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*Identified compound **210527** (see **MDL-10007F**) Drug Data Report 1994, 016(08): 0769.

T-98475**258388**

3-(*N*-Benzyl-*N*-methylaminomethyl)-7-(2,6-difluorobenzyl)-2-[4-(isobutyramido)phenyl]-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid isopropyl ester hydrochloride



C37 H37 F2 N3 O4 S . HCl; Mol wt: 694.2392

ACTION – Potent, orally active, nonpeptide antagonist of the human luteinizing hormone-releasing hormone (LHRH) receptor (K_i = 0.2 nM against [125 I]-leuprorelin binding to the cloned human receptor), with 20- and 300-fold selectivity, respectively, over monkey and rat LHRH receptors and no interaction with other G-protein-coupled receptors. In a functional assay, compound decreased LH release induced by LHRH in cynomolgus monkey pituitary cells with an IC_{50} value of about 100 nM. Orally administered (60 mg/kg) compound induced high (> 70%) and long-lasting (> 10 h) inhibition of plasma LH levels in castrated cynomolgus monkeys. Potentially useful for the treatment of sex hormone-dependent pathologies such as prostate and breast cancer, endometriosis, uterine leiomyoma and precocious puberty.

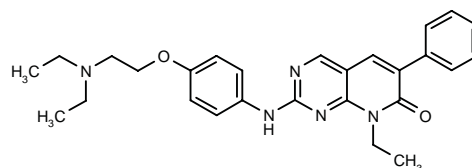
SOURCE – Takeda.**REFERENCES**

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2. Suzuki, N. and Furuya, S. (Takeda Chemical Industries, Ltd.) *Combined use of GnRH agonist and antagonist*. WO 9740846.
3. Suzuki, N. et al. (Takeda Chemical Industries, Ltd.) *Inhibitor of prolactin production*. EP 781774, JP 97216823.
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5. Furuya, S. et al. *Non-peptide LH-RH antagonists*. 17th Symp Med Chem (Nov 19-21, Tsukuba) 1997, Abst 2-P-34.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

269896

2-[4-[2-(Diethylamino)ethoxy]phenylamino]-8-ethyl-6-phenyl-8H-pyrido[2,3-*d*]pyrimidin-7-one



C27 H31 N5 O2; Mol wt: 457.5749

M.p. 125-6 °C.

ACTION – Antineoplastic agent, a potent inhibitor of platelet-derived growth factor (PDGF) receptor, fibroblast growth factor (FGF) receptor and c-src tyrosine kinases (IC_{50} = 31, and 88 and 31 nM, respectively); it was active at nanomolar concentrations in a variety of PDGF-dependent cellular assays such as PDGF-stimulated autophosphorylation in rat glioma C6 cells (IC_{50} = 58 nM) and C6 cell proliferation (IC_{50} = 7.2 μ M). In tumor model systems in mice such as C6 glioma and PDGF-transfected NHI 3T3 cells, compound at doses of 20 and 40 mg/kg strongly inhibited tumor growth without gross toxicity or weight loss, and it was also effective against prostate epithelial cell DU-145 xenografts. Favorable pharmacokinetics were observed in rats following single oral doses.

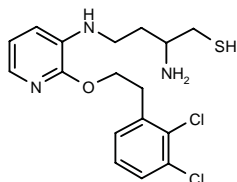
SOURCE – Warner-Lambert.

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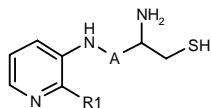
270099

2-Amino-4-[2-[2-(2,3-dichlorophenyl)ethoxy]-3-pyridinyl-amino]-1-butanethiol



C17 H21 Cl2 N3 O S; Mol wt: 386.3449

ACTION – Agent for the treatment of inflammatory and proliferative diseases that inhibits T-cell proliferation and protein farnesyltransferase (IC_{50} = 25 nM using recombinant human enzyme). Within this series of specifically claimed aminopyridine derivatives, the following are also included:



Compound	R1	A	Formula
270100	1-Naph-CH ₂ CH ₂ O	-(CH ₂) ₂ -	C ₂₁ H ₂₅ N ₃ OS
270101	2-thienyl-CH ₂ CH ₂ O	-(CH ₂) ₂ -	C ₁₅ H ₂₁ N ₃ OS ₂
270102	3-benzothieryl-CH ₂ CH ₂ O	-(CH ₂) ₂ -	C ₁₉ H ₂₃ N ₃ OS ₂
270103	2,3-(Cl)2-PhCH ₂ CH ₂ O	-CH ₂ -	C ₁₆ H ₁₉ Cl ₂ N ₃ OS
270104	N(Me)CH ₂ H ₂ Ph	-CH ₂ -	C ₁₇ H ₂₄ N ₄ S

SOURCE – Ferring.

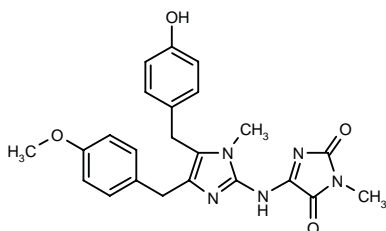
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NAAMIDINE A

269047

4-[5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazol-2-ylamino]-1-methyl-1H-imidazole-2,5-dione



C23 H23 N5 O4; Mol wt: 433.4657

ACTION – Alkaloid extracted from the Fijian sponge *Leucetta* sp., that selectively inhibits the epidermal growth factor (EGF)-mediated mitogenic response in NIH 3T3 cells (IC_{50} = 11.3 μ M vs. 242 μ M for inhibition of insulin receptor-mediated mitogenesis). *In vivo*, compound showed antitumor activity in athymic nude mice bearing EGF-dependent squamous cell carcinoma A431, producing 85% growth inhibition at the maximum tolerated dose of 25 mg/kg, although it was toxic (2 mice died) at the dose of 50 mg/kg. Preliminary studies indicated that it does not inhibit the binding of EGF to the receptor and does not affect the catalytic activity of c-src tyrosine kinase.

SOURCES – Bristol-Myers Squibb; University of Utah, Salt Lake City, UT (US).

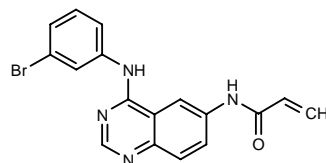
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PD-168393*1-5

264942

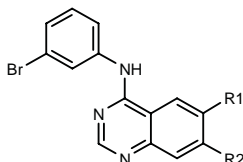
N-[4-(3-Bromophenylamino)quinazolin-6-yl]-2-propenamide



C17 H13 Br N4 O; Mol wt: 369.2207

ACTION – Potent, specific and irreversible inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase, as demonstrated against isolated enzyme (IC_{50} = 0.70-0.84 nM) and against EGF receptor-induced tyrosine phosphorylation in human epidermoid carcinoma A431 cells (IC_{50} = 4.3 nM), with no activity against insulin receptor, platelet-derived growth factor (PDGF) receptor tyrosine kinase, basic fibroblast growth factor (bFGF) receptor tyrosine kinase or protein kinase C (PKC) at concentrations of > 50,000 nM. In nude mice bearing

advanced-stage A431 xenografts, compound produced significant tumor growth delays when given i.p. on various dosing schedules, with tumor regression in all 6 mice treated at doses of 28 and 47 mg/kg/day i.p. on days 7-11, 13-18 and 21-25; comparable antitumor activity and reduced toxicity were noted upon oral administration. PD-168393 was also effective against non-small cell lung cancer H125 and human breast carcinoma MCF-7 following i.p. and p.o. administration, producing tumor growth and/or tumor stasis. This compound, however, is relatively insoluble. The following related anilinoquinazolinones are reversible inhibitors of the enzyme:



Compound	R1	R2	Formula
PD-174265 [260353] ^{1,3,4}	NHCOEt	H	C ₁₇ H ₁₅ BrN ₄ O
PD-160879 [269420] ^{1,3}	H	NHCOCH=CHMe	C ₁₈ H ₁₅ BrN ₄ O

SOURCES – American Home Products; Warner-Lambert.

REFERENCES

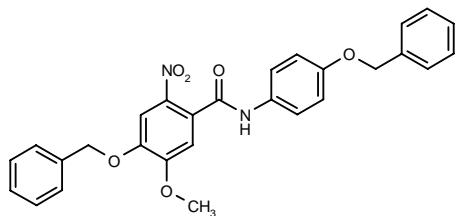
- Bridges, A.J. et al. (Warner-Lambert Co.) *Irreversible inhibitors of tyrosine kinases*. WO 9738983.
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- Patmore, S.J. et al. *In vivo evaluation of the irreversible EGF receptor tyrosine kinase inhibitor PD 168393*. Proc Amer Assoc Cancer Res 1998, Abst 3805.

*Identified compound **264942** (see **264472**) Drug Data Report 1998, 020(07): 0630.

ANGIOGENESIS INHIBITORS

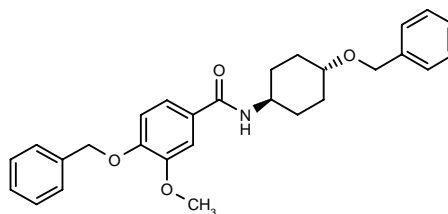
269709

4-Benzyloxy-*N*-(4-benzyloxyphenyl)-5-methoxy-2-nitrobenzamide

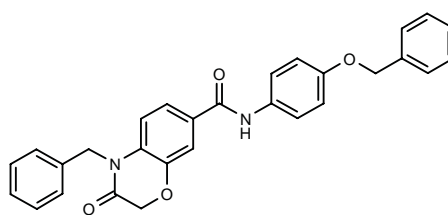


C28 H24 N2 O6; Mol wt: 484.5056

ACTION – Agent with neovascularization-inhibitory properties whose activity was tested *in vivo* in a murine air pouch model, giving 37 and 48% inhibition of neovascularization at 10 and 100 mg/kg p.o., respectively. A representative compound from a series of benzamido derivatives, wherein the following are also included:



269710: C28 H31 N O4



269711: C29 H24 N2 O4

SOURCE – Japan Tobacco.

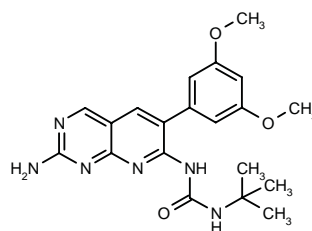
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PD-166866

269256

N-[2-Amino-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]-*N'*-(*tert*-butyl)urea



C20 H24 N6 O3; Mol wt: 396.4486

Off-white solid, m.p. > 250 °C (decomp.).

ACTION – Antiproliferative and antiangiogenic agent, a potent and selective inhibitor of human fibroblast growth factor-1 receptor (FGFR) tyrosine kinase (IC₅₀ = 52.4 ± 0.1 nM), with no effect against a range of other receptor tyrosine kinases, MAP kinase, protein kinase C or cdk4 at up to 50 μM. It selectively inhibited basic fibroblast growth factor (bFGF)-mediated receptor autophosphorylation in FGFR-expressing NIH 3T3 cells (IC₅₀ = 10.8 nM) and FGFR autophosphorylation in L6 cells (IC₅₀ = 3.1 nM). PD-166866 inhibited bFGF-stimulated L6 cell growth with an IC₅₀ of 24 nM, whereas it had little effect against platelet-derived growth factor-BB (PDGF-BB)-stimulated growth or serum-stimulated vascular smooth muscle cell proliferation. It also potently inhibited angiogenesis in cultured human placental artery fragments, with about 50% inhibition at 470 nM and almost complete inhibition at 25 μM. Potentially useful for inhibiting tumor and atherosclerotic plaque neovascularization.

SOURCE – Warner-Lambert.

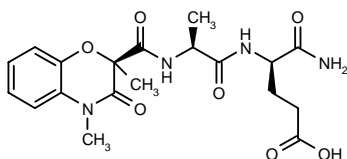
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1. Connolly, C.J.C. et al. *Discovery and structure-activity studies of a novel series of pyrido[2,3-d]pyrimidine tyrosine kinase inhibitors*. Bioorg Med Chem Lett 1997, 7(18): 2415.
2. Hamby, J.M. et al. *Structure-activity relationships for a novel series of pyrido[2,3-d]-pyrimidine tyrosine kinase inhibitors*. J Med Chem 1997, 40(15): 2296.
3. Panek, R.L. et al. *In vitro biological characterization of antiangiogenic effects of PD 166866, a selective inhibitor of the FGF-1 receptor tyrosine kinase*. J Pharmacol Exp Ther 1998, 286(1): 569.
4. Trumpp-Kallmeyer, S. et al. *Development of a binding model to protein tyrosine kinases for substituted pyrido[2,3-d]pyrimidine inhibitors*. J Med Chem 1998, 41(11): 1752.

OTHER ONCOLYTIC DRUGS

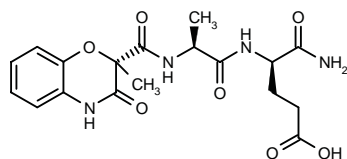
269509

N-[2(*S*),4-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylcarbonyl]-L-alanyl-D-isoglutamine



C19 H24 N4 O7; Mol wt: 420.4196

ACTION – Immunostimulant and antineoplastic agent with potential in the treatment or prevention of the immunosuppressive side effects of cancer chemotherapy, in the treatment of infections in immunocompromised patients, as well as for the treatment of certain types of cancer such as melanoma. In mice bearing melanoma B16, compound produced complete regression of tumors in 1 of 9 animals and slowed tumor growth in the remaining animals at 10 mg/kg/day i.p. x 5 days. Another specifically claimed compound from this series of heterocyclic acyldipeptides is:



269510: C18 H22 N4 O7

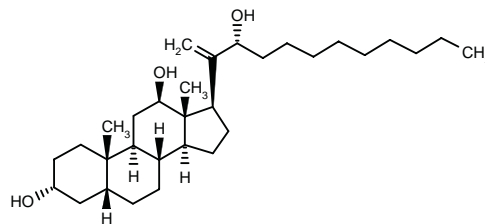
SOURCES – LEK; University of Ljubljana, Ljubljana (SI).

REFERENCES

1. Kikelj, D. et al. (LEK Pharmaceutical and Chemical Co.;University of Ljubljana) *Heterocyclic acyldipeptides, processes for the preparation thereof and pharmaceutical compsns. containing the same*. US 5824652.

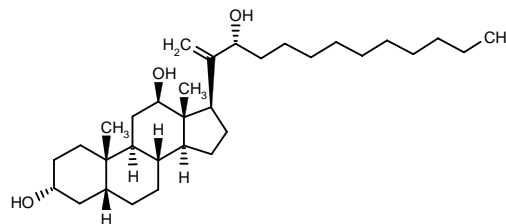
269906

20-[1(*R*)-Hydroxydecyl]-20-pregnen-3 α ,12 β -diol



C31 H54 O3; Mol wt: 474.7646

ACTION – Antineoplastic agent proven to increase survival time of mice bearing L1210 leukemia (T/C x 100 = 185% at 1.6 mg/kg/day i.p. x 5 days). Another compound from this series of *cis*-sterol derivatives is:



269907: C32 H56 O3

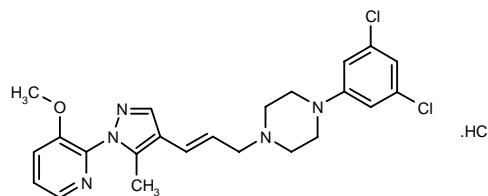
SOURCE – Taisho.

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1. Asanuma, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Cis-sterol cpds*. JP 98251294.

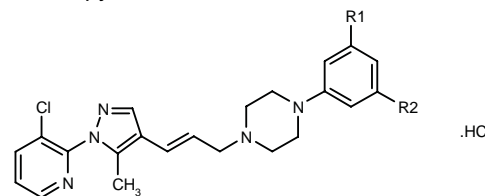
270424

1-(3,5-Dichlorophenyl)-4-[3-[1-(3-methoxy-2-pyridinyl)-5-methyl-1*H*-pyrazol-4-yl]-2(*E*)-propenyl]piperazine hydrochloride



C23 H25 Cl2 N5 O . HCl; Mol wt: 494.8514

ACTION – Antineoplastic agent with potent cytotoxicity against human lung cancer PC-6 and PC-12 cells (GI₅₀ = 4.93 and 38.3 ng/ml, respectively). Other compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	Formula
270425	Cl	F	C ₂₂ H ₂₂ Cl ₂ FN ₅ .HCl
270426	F	F	C ₂₂ H ₂₂ ClF ₂ N ₅ .HCl
270427	Cl	Cl	C ₂₂ H ₂₂ Cl ₃ N ₅ .HCl
270428	H	Cl	C ₂₂ H ₂₃ Cl ₂ N ₅ .HCl

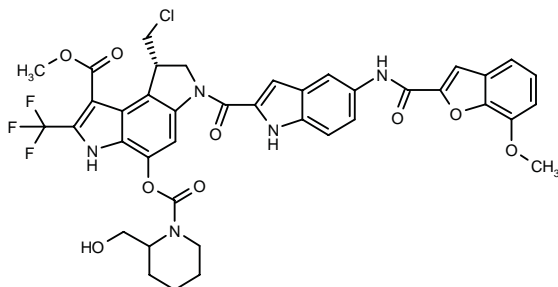
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Ejima, A. and Ohsuki, S. (Daiichi Pharmaceutical Co., Ltd.) *Pyrazole derivs.* WO 9832739.

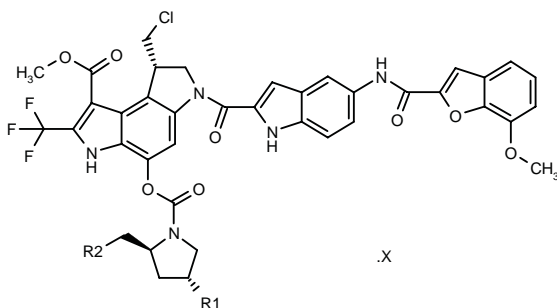
270463

8(S)-(Chloromethyl)-4-[2-(hydroxymethyl)piperidin-1-yl-carbonyloxy]-6-[5-(7-methoxybenzofuran-2-ylcarbox-amido)-1H-indol-2-ylcarbonyl]-2-(trifluoromethyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-1-carboxylic acid methyl ester



C40 H35 Cl F3 N5 O9; Mol wt: 822.1895

ACTION – Antineoplastic and antibacterial agent proven to potently inhibit the growth of doxorubicin-resistant M5076 tumors implanted s.c. in mice, giving a T/C value of 0.01 at a dose of 1.0 mg/kg i.v. A representative compound from a series of pyrroloindole derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
270464	H	OH		C ₃₉ H ₃₃ ClF ₃ N ₅ O ₉
270465	OH	OH		C ₃₉ H ₃₃ ClF ₃ N ₅ O ₁₀
270466	H	1-pyrrolidinyl	HCl	C ₄₃ H ₄₀ ClF ₃ N ₆ O ₈ ·HCl

SOURCES – Kyorin; Sagami.

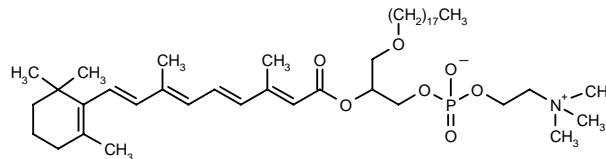
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CPR-2003

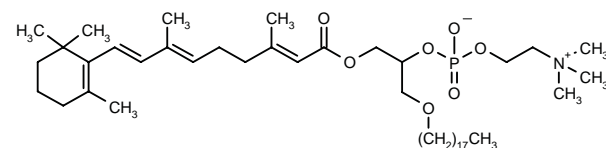
269835

2-O-[3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2(E),4(E),6(E),8(E)-nonatetraenoyl]-1-O-octadecyl-3-glycerophosphocholine



C46 H82 N O7 P; Mol wt: 792.1278

ACTION – Antineoplastic, antipsoriatic and antiinflammatory agent with marked antileukemic activity; it was also shown to inhibit keratinocyte proliferation, as well as the release of cytokines in activated macrophages (about 50% inhibition at 3 μM). Another specifically claimed compound within this series of retinoid glycerol phospholipid conjugates is:



CPR-2004 [269836]: C46 H84 N O7 P

SOURCE – Clarion.

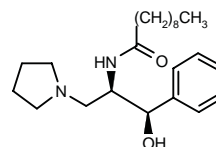
REFERENCES

1. Peterson, A.C. et al. (Clarion Pharmaceuticals Inc.) *Retinoid glycerol phospholipid conjugates.* US 5827836.

D-THREO-PDPP

269198

(R,R)-N-[2-Hydroxy-2-phenyl-1-(1-pyrrolidinylmethyl)-ethyl]decanamide



C23 H38 N2 O2; Mol wt: 374.5652

ACTION – Inhibitor of ceramide glucosyltransferase with potential in the treatment of cancer or metabolic diseases such as Gaucher's disease and Tay-Sachs disease.

SOURCE – Seikagaku.

REFERENCES

1. Jinbo, M. et al. (Seikagaku Corp.) *Amino alcohol deriv. and method for preparing the same.* EP 782992.

2. Miura, T. et al. *Synthesis and evaluation of morpholino- and pyrrolidinospingolipids as inhibitors of glucosylceramide synthase.* Bioorg Med Chem 1998, 6(9): 1481.

CANCER GENE THERAPY**ISIS-10639****270040**

20-Mer antisense phosphorothioate oligonucleotide targeted to the human *c-fos* gene whose sequence is: 5'-AAGTCCTTGAGGCCACAGC-3'

ACTION – Antisense phosphorothioate oligonucleotide targeted to the human transcription factor activating protein 1 (AP-1) *c-fos* subunit and proven to selectively reduce *c-fos* mRNA expression in A459 cells (91% at 400 nM). *In vivo* in nude mice bearing human tumor A549 xenografts, daily i.v. administration at a dose of 25 mg/kg for 3 weeks was associated with a significant reduction in the tumor growth rate. Potentially useful in the treatment and diagnosis of tumor metastasis.

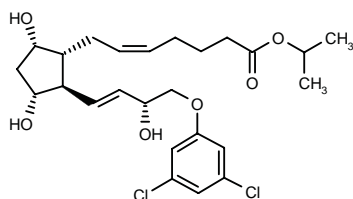
SOURCE – Isis Pharmaceuticals.

REFERENCES

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OCULAR MEDICATIONS**ANTIGLAUCOMA AGENTS****269651**

16-(3,5-Dichlorophenoxy)-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester



C25 H34 Cl2 O6; Mol wt: 501.4436

ACTION – Prostaglandin with intraocular pressure (IOP)-lowering activity superior to latanoprost in anesthetized monkeys, reducing IOP by 1.0, 3.9 and 3.4 mmHg, respectively, at 2, 4 and 6 h following intraocular instillation of 20 µl of a 0.1% w/v solution (−0.6, −2.6 and −2.3 mmHg, respectively, for latanoprost).

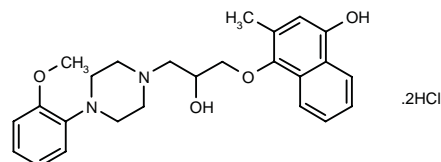
SOURCES – Asahi Glass; Santen.

REFERENCES

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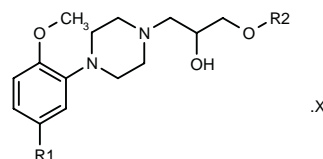
270316

4-[2-Hydroxy-3-[4-(2-methoxyphenyl)piperazin-1-yl]-propoxy]-3-methyl-1-naphthol dihydrochloride



C25 H30 N2 O4 . 2HCl; Mol wt: 495.4438

ACTION – Antiglaucoma agent with free radical-scavenging activity and significant intraocular pressure (IOP)-lowering activity in anesthetized rabbits administered eye drops (0.5%, 50 µl). Antihypertensive activity was also demonstrated after oral administration to spontaneously hypertensive rats at a dose of 30 mg/kg. Within this series of hydroquinone derivatives, the following are also included:



Compound	R1	R2	X	Formula
270317	H	3-Me-4-OH-1-Naph		C ₂₅ H ₃₀ N ₂ O ₄
270318	H	4-OH-3,5-(Me)2-Ph	2HCl	C ₂₂ H ₃₀ N ₂ O ₄ .2HCl
270319	H	3-t-Bu-4-OH-Ph	HCl	C ₂₄ H ₃₄ N ₂ O ₄ .HCl
270320	H	2,3-(Me)2-4-OH-Ph	HCl	C ₂₂ H ₃₀ N ₂ O ₄ .HCl
270321	H	2,3,5-(Me)3-4-OH-Ph		C ₂₃ H ₃₂ N ₂ O ₄
270322	OMe	4-OH-Ph	2HCl	C ₂₁ H ₂₈ N ₂ O ₅ .2HCl

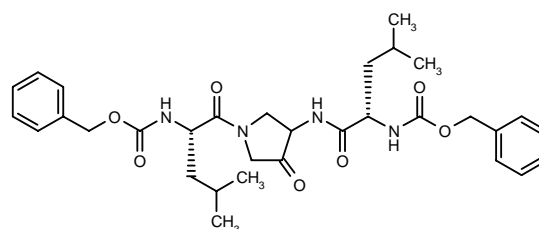
SOURCE – Senju.

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METABOLIC DRUGS**TREATMENT OF BONE DISEASES****268327¹⁻³**

N-[1(*S*)-[3-(*N*-Benzyloxycarbonyl-L-leucylamino)-4-oxopyrrolidin-1-ylcarbonyl]-3-methylbutyl]carbamic acid benzyl ester



C32 H42 N4 O7; Mol wt: 594.7048

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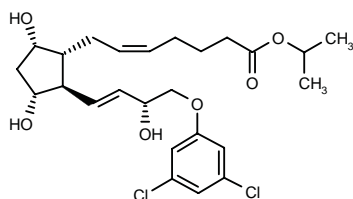
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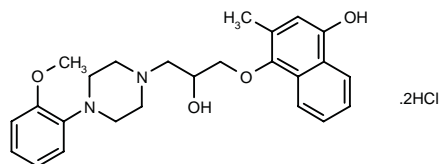
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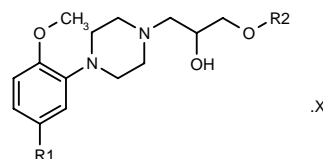
270316

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270320	H	2,3-(Me)2-4-OH-Ph	HCl	C ₂₂ H ₃₀ N ₂ O ₄ .HCl
270321	H	2,3,5-(Me)3-4-OH-Ph		C ₂₃ H ₃₂ N ₂ O ₄
270322	OMe	4-OH-Ph	2HCl	C ₂₁ H ₂₈ N ₂ O ₅ .2HCl

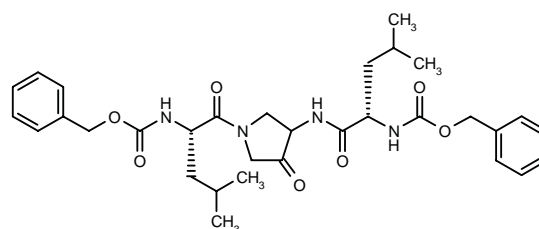
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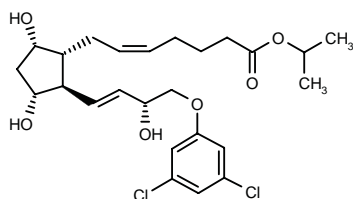
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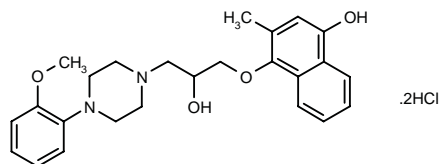
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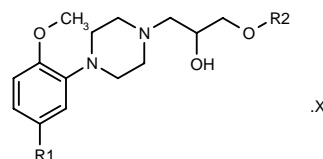
270316

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C25 H30 N2 O4 . 2HCl; Mol wt: 495.4438

ACTION – Antiglaucoma agent with free radical-scavenging activity and significant intraocular pressure (IOP)-lowering activity in anesthetized rabbits administered eye drops (0.5%, 50 µl). Antihypertensive activity was also demonstrated after oral administration to spontaneously hypertensive rats at a dose of 30 mg/kg. Within this series of hydroquinone derivatives, the following are also included:



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270317	H	3-Me-4-OH-1-Naph		C ₂₅ H ₃₀ N ₂ O ₄
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270320	H	2,3-(Me)2-4-OH-Ph	HCl	C ₂₂ H ₃₀ N ₂ O ₄ .HCl
270321	H	2,3,5-(Me)3-4-OH-Ph		C ₂₃ H ₃₂ N ₂ O ₄
270322	OMe	4-OH-Ph	2HCl	C ₂₁ H ₂₈ N ₂ O ₅ .2HCl

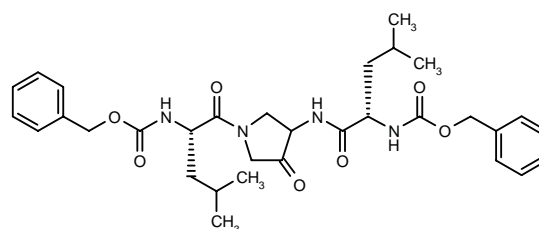
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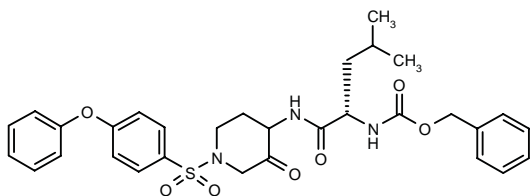
METABOLIC DRUGS**TREATMENT OF BONE DISEASES****268327¹⁻³**

N-[1(*S*)-[3-(*N*-Benzyloxycarbonyl-L-leucylamino)-4-oxopyrrolidin-1-ylcarbonyl]-3-methylbutyl]carbamic acid benzyl ester



C32 H42 N4 O7; Mol wt: 594.7048

ACTION – Potent and selective inhibitor of the cysteine protease cathepsin K ($K_i = 2.3$ nM) with over 1000-fold selectivity versus cathepsin B and 39-fold selectivity versus cathepsin L. Potentially useful in the treatment of diseases characterized by excess bone resorption. Another compound from this series of conformationally constrained 1,3-diaminoketones is:



268328^{2,3}: C₃₁ H₃₅ N₃ O₇ S

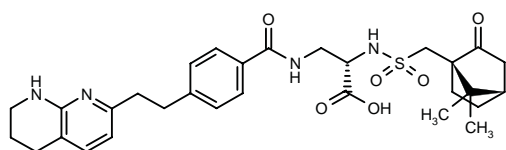
SOURCE – SmithKline Beecham.

REFERENCES

1. Abdel-Mequid, S.S. et al. (SmithKline Beecham Corp.) *Method of inhibiting cathepsin K*. WO 9716177.
2. Marquis, R.W. Jr. et al. (SmithKline Beecham plc) *Inhibitors of cysteine protease*. WO 9805336.
3. Marquis, R.W. et al. *Conformationally constrained 1,3-diamino ketones: A series of potent inhibitors of the cysteine protease cathepsin K*. J Med Chem 1998, 41(19): 3563.

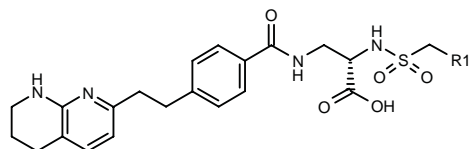
270117

2(*S*)-[[(1*R*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-ylmethylsulfonamido]-3-[4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]benzamido]propionic acid



C₃₀ H₃₈ N₄ O₆ S; Mol wt: 582.7182

ACTION – Nonpeptide $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation and viral infections. Other specifically claimed compounds include the following:



Compound	R1	Formula
270118	2-adamantyl	C ₃₁ H ₄₀ N ₄ O ₅ S
270119	(1 <i>S</i> ,5 <i>S</i>)-6,6-(Me) ₂ -bicyclo[3.1.1]hept-2-en-2-yl-CH ₂	C ₃₁ H ₄₀ N ₄ O ₅ S
270120	(1 <i>S</i> ,4 <i>R</i>)-7,7(Me) ₂ -2-oxo-bicyclo[2.2.1]hept-1-yl	C ₃₀ H ₃₈ N ₄ O ₆ S

SOURCE – Merck & Co.

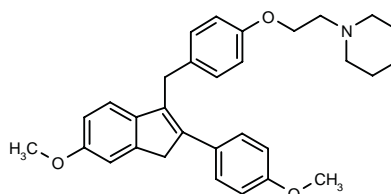
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1. Duggan, M.E. (Merck & Co., Inc.) *Integrin antagonists*. WO 9831359.

TREATMENT OF LIPOPROTEIN DISORDERS

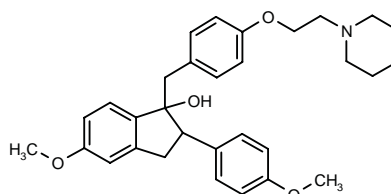
270239

1-[2-[4-[6-Methoxy-2-(4-methoxyphenyl)-1*H*-inden-3-ylmethyl]phenoxy]ethyl]piperidine

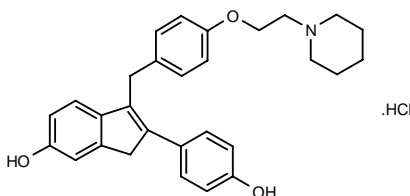


C₃₁ H₃₅ N O₃; Mol wt: 469.6215

ACTION – Selective estrogen receptor modulator (SERM) for the treatment of osteoporosis and cardiovascular diseases, particularly hyperlipidemia, in women. Compound decreased serum cholesterol levels in ovariectomized rats without exhibiting undesirable side effects (e.g., increase in uterine weight) characteristic of estrogenic drugs such as 17 α -ethinylestradiol. Within this series of indene derivatives, the following are also included:



270240: C₃₁ H₃₇ N O₄



270241: C₂₉ H₃₁ N O₃. HCl

SOURCE – Lilly.

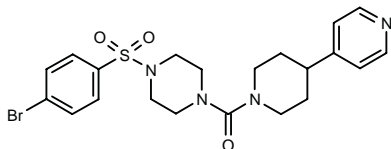
REFERENCES

1. Bryant, H.U. et al. (Eli Lilly and Company) *Indene cpds. having activity as SERMs*. EP 873992.

270911

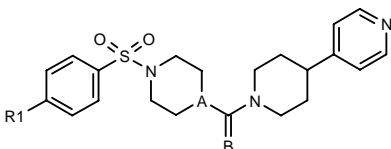
1-(4-Bromophenylsulfonyl)-4-[4-(4-pyridinyl)piperidin-1-ylcarbonyl]piperazine

[4-(4-Bromophenylsulfonyl)-1-piperazinyl][4-(4-pyridinyl)-1-piperidinyl]methanone



C21 H25 Br N4 O3 S; Mol wt: 493.4235

ACTION – Hypocholesterolemic and antiatherosclerotic agent, an inhibitor of lanosterol synthase (94% inhibition of enzyme from rat liver microsomes at 0.1 μ M). *In vivo*, compound gave 85% inhibition of cholesterol biosynthesis in rats at 2 mg/kg p.o. Other heterocyclic compounds include the following:



Compound	R1	A	B	Formula
270912	Br	CH	O	C ₂₂ H ₂₆ BrN ₃ O ₃ S
270913	Cl	N	O	C ₂₁ H ₂₅ ClN ₄ O ₃ S
270914	CF ₃	CH	H ₂	C ₂₃ H ₂₈ F ₃ N ₃ O ₂ S

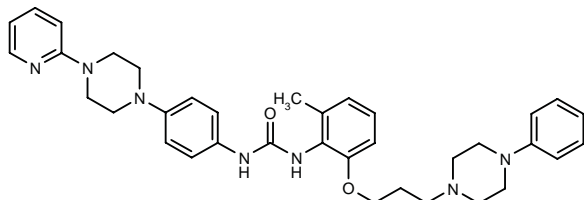
SOURCE – Zeneca.

REFERENCES

1. Brown, G.R. et al. (Zeneca Ltd.) *Heterocyclic cpds. useful as oxido-squalene cyclase inhibitors*. WO 9835959.

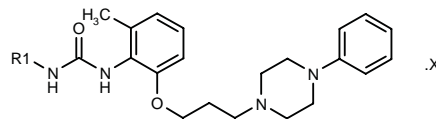
270964

N-[2-Methyl-6-[3-(4-phenyl-1-piperazinyl)propoxy]phenyl]-*N'*-[4-[4-(2-pyridinyl)-1-piperazinyl]phenyl]urea



C36 H43 N7 O2; Mol wt: 605.7827

ACTION – Hypolipidemic and antiatherosclerotic agent with ACAT-inhibitory activity, giving IC₅₀ values of 0.03 and 0.14 μ M, respectively, for inhibition of ACAT from human HepG2 cells and rat macrophages. Other compounds from this series of urea derivatives include the following:



Compound	R1	X	Formula
270965	4-(2-Pyr-CH ₂ O)-PhCH ₂		C ₃₄ H ₃₉ N ₅ O ₃
270966	4-(2-Pyr-CH ₂ O)-PhCH ₂	2HCl	C ₃₄ H ₃₉ N ₅ O ₃ ·2HCl
270967	4-(1-imidazolyl)-Ph	HCl	C ₂₉ H ₃₅ N ₆ O ₂ ·HCl
270968	4-[4-(2-Pyr)-Piz]-Ph	2HCl	C ₃₆ H ₄₃ N ₇ O ₂ ·2HCl

SOURCE – Mitsubishi Chemical.

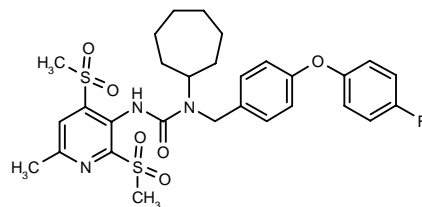
REFERENCES

1. Inoue, S. et al. (Mitsubishi Chemical Corp.) *Urea derivs*. JP 98306078.

FR-190809

269901

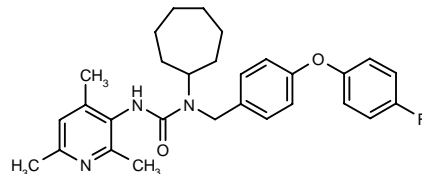
N-Cycloheptyl-*N*-[4-(4-fluorophenoxy)benzyl]-*N'*-[6-methyl-2,4-bis(methylsulfonyl)pyridin-3-yl]urea



C29 H34 F N3 O6 S2; Mol wt: 603.7326

M.p. 129-30 °C.

ACTION – Hypolipidemic agent, an inhibitor of ACAT (IC₅₀ = 45 nM against rabbit intestinal ACAT) shown to inhibit acetylated LDL-induced accumulation of cholesteryl esters in murine peritoneal macrophages (IC₅₀ = 215 nM). In cholesterol-fed rats, compound reduced blood cholesterol levels with an ED₅₀ of 0.068 mg/kg in the diet and 0.63 mg/kg p.o. No signs of adrenal toxicity were noted in rabbits at a dose of 5 mg/kg i.v. Another related compound is:



FR-186485 [269902]: C29 H34 F N3 O2

SOURCE – Fujisawa.

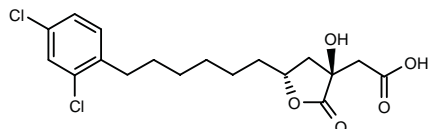
REFERENCES

1. Terasawa, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Urea derivs. and their use as ACAT-inhibitors*. JP 98510512, WO 9610559.

2. Tanaka, A. et al. *Inhibitors of acyl-CoA:cholesterol O-acyltransferase. 3. Discovery of a novel series of N-alkyl-N-[(fluorophenoxy)benzyl]-N'-arylsureas with weak toxicological effects on adrenal glands*. J Med Chem 1998, 41(22): 4408.

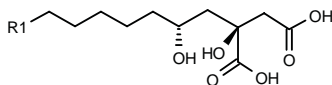
SB-204990¹⁻⁴**268329**

(±)-(3*R**,5*S**)-5-[6-(2,4-Dichlorophenyl)hexyl]-3-hydroxy-2-oxo-2,3,4,5-tetrahydrofuran-3-acetic acid



C18 H22 Cl2 O5; Mol wt: 389.2728

ACTION – Hypolipidemic and antiatherosclerotic agent, a potent inhibitor of cholesterol and fatty acid synthesis that acts by blocking ATP citrate (*pro*-3*S*)-lyase ($K_i = 1 \mu\text{M}$ against human enzyme). Compound at 30 μM induced strong and long-lasting (up to 16 h) inhibition of both cholesterol (91%) and fatty acid synthesis (82%) in HepG2 cells. When administered to rats in the diet at 0.05-0.25% w/w for 1 week and to dogs orally at 25 mg/kg/day for 15 days, SB-204990 produced a significant and sustained decrease in fasting plasma cholesterol and triglyceride levels of up to 46 and 80% (in rats), respectively, and 23 and 38% (in dogs), respectively. In APOE*3-Leiden transgenic mice that develop hyperlipidemia and atherosclerosis, compound (0.1 and 0.2% w/w in the diet for 2 weeks) reduced plasma cholesterol and plasma triglycerides by 29 and 43%, respectively. Other related compounds are:



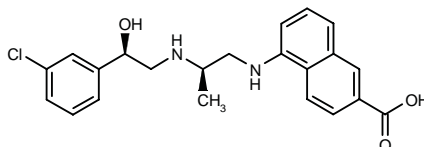
SOURCE – SmithKline Beecham.

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- Gribble, A.D. et al. (SmithKline Beecham plc) *Phenyl derivative as inhibitors of ATP citrate lyase*. EP 639187, WO 9322304.
- Gribble, A.D. et al. *ATP-citrate lyase as a target for hypolipidemic intervention. 2. Synthesis and evaluation of (3*R**,5*S**)-ω-substituted-3-carboxy-3,5-dihydroxy-alkanoic acids and their γ-lactone prodrugs as inhibitors of the enzyme in vitro and in vivo*. J Med Chem 1998, 41(19): 3582.
- Pearce, N.J. et al. *The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Hypolipidaemic effects of SB-204990, a lactone prodrug of the potent ATP citrate-lyase inhibitor SB-201076*. Biochem J 1998, 334(1): 113.
- van Vlijmen, B.J.M. et al. *Apolipoprotein E*3-Leiden transgenic mice as a test model for hypolipidaemic drugs*. Arzneimittel-Forschung Drug Res 1998, 48(4): 396.

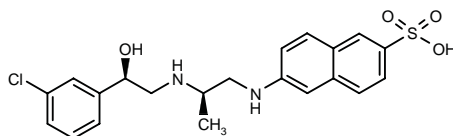
TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS
269622

5-[2(*R*)-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]-propylamino]naphthalene-2-carboxylic acid



C22 H23 Cl N2 O3; Mol wt: 398.8877

ACTION – Atypical (β_3) adrenoceptor agonist with potential utility in the treatment of obesity and diabetes and certain gastrointestinal disorders. Other specifically claimed naphthalene sulfonic or carboxylic acid derivatives include the following:



269623: C21 H23 Cl N2 O4 S

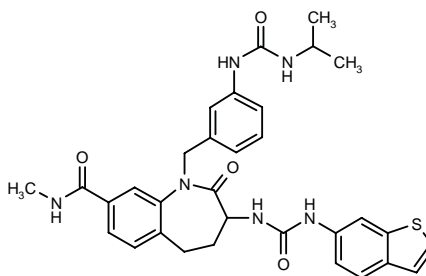
SOURCE – Glaxo Wellcome.

REFERENCES

- Deaton, D.N. and McFadyen, R.B. (Glaxo Wellcome plc) *Naphthalenesulphonic or carboxylic acids and their use as atypical β-adrenoceptor agonists*. WO 9843953.

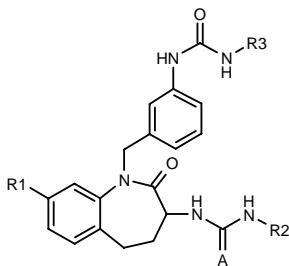
270297

3-[3-(Benzo[*b*]thien-6-yl)ureido]-1-[3-(3-isopropylureido)-benzyl]-*N*-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-8-carboxamide



C32 H34 N6 O4 S; Mol wt: 598.7246

ACTION – Agent for the treatment of eating disorders, myocardial infarction, angina and hypertension, a neuropeptide Y (NPY) Y_1 receptor antagonist ($\text{IC}_{50} = 0.0032 \mu\text{M}$ against [^{125}I]-peptide YY binding in SK-N-MC cells). Other particularly potent compounds within this series of benzolactam derivatives include the following:



Compound	R1	R2	R3	A	Formula
270298	H	4-OH-Ph	i-Pr	N(Me)	C ₂₉ H ₃₄ N ₆ O ₃
270299	H	6-benzothiazolyl	i-Pr	O	C ₂₉ H ₃₀ N ₆ O ₃ S
270300	H	4-OH-Ph	i-Pr	NH	C ₂₈ H ₃₂ N ₆ O ₃
270301	H	2-F-Ph	i-Pr	O	C ₂₈ H ₃₀ FN ₆ O ₃
270302	H	6-benzothieryl	i-Pr	O	C ₃₀ H ₃₁ N ₆ O ₃ S
270303	H	6-benzothiazolyl	i-Pr	N(Me)	C ₃₀ H ₃₃ N ₇ O ₂ S
270304	CO ₂ Me	6-benzothieryl	i-Pr	O	C ₃₂ H ₃₃ N ₆ O ₅ S
270305	H	6-benzothieryl	N(Me) ₂	O	C ₂₉ H ₃₀ N ₆ O ₃ S

SOURCE – Shionogi.

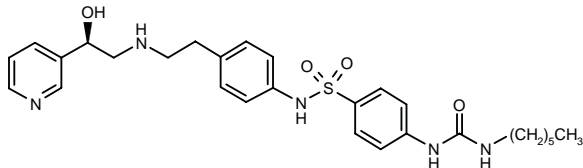
REFERENCES

1. Hagishita, S. et al. (Shionogi & Co. Ltd.) *New benzolactam derivs. and medicinal compsns. containing the same.* WO 9835941, WO 9841510.

L-757793

270085

4-(3-Hexylureido)-N-[4-[2-[2(R)-hydroxy-2-(3-pyridinyl)-ethylamino]ethyl]phenyl]benzenesulfonamide



C28 H37 N5 O4 S; Mol wt: 539.6973

ACTION – Potent and selective human β_3 -adrenoceptor agonist (EC_{50} = 6.3 nM for adenylyl cyclase activation; 70% activation vs. isoproterenol) with 1300- and 500-fold selectivity over β_1 - and β_2 -adrenoceptors, respectively (IC_{50} = 8000 and 3000 nM, respectively, in binding studies using cloned human receptors). *In vivo* in rhesus monkeys, compound stimulated lipolysis (ED_{50} = 0.2 mg/kg i.v.), with a maximum response equivalent to that elicited by isoproterenol. However, it has poor oral bioavailability and further studies are in progress with the aim of preparing a compound with the biological profile of L-757793 and improved pharmacokinetic properties.

SOURCE – Merck & Co.

REFERENCES

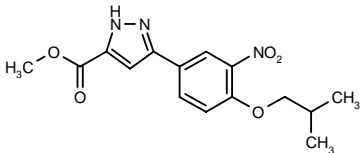
1. Fisher, M.H. et al. (Merck & Co., Inc.) *Substd. sulfonamides as selective β_3 agonists for the treatment of diabetes and obesity.* EP 757674, JP 97512275, US 5541197, US 5561142, WO 9529159.

2. Naylor, E.M. et al. *3-Pyridylethanolamines: Potent and selective human β_3 adrenergic receptor agonists.* Bioorg Med Chem Lett 1998, 8(21): 3087.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

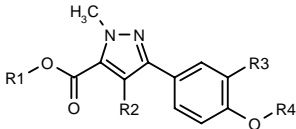
270983

3-(4-Isobutoxy-3-nitrophenyl)-1 H-pyrazole-5-carboxylic acid methyl ester



C15 H17 N3 O5; Mol wt: 319.3153

ACTION – Potent xanthine oxidase inhibitor (IC_{50} = 30 nM or less vs. 300 nM for allopurinol) for the treatment of gout and hyperuricemia. Compound is reported to decrease uric acid levels in several animal models. Within this series of 3-phenylpyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
270984	H	H	CN	H	C ₁₂ H ₉ N ₃ O ₃
270985	H	H	CN	(CH ₂) ₃ Ph	C ₂₁ H ₁₉ N ₃ O ₃
270986	i-BuCH ₂	H	NO ₂	i-BuCH ₂	C ₂₁ H ₂₉ N ₃ O ₅
270987	H	H	CN	CH ₂ CH ₂ N(Me) ₂	C ₁₈ H ₁₈ N ₄ O ₃
270988	Me	Cl	CN	t-BuCH ₂	C ₁₈ H ₂₀ ClN ₃ O ₃

SOURCE – Yoshitomi.

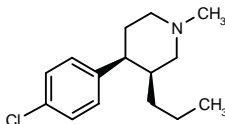
REFERENCES

1. Morimoto, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *3-Phenylpyrazole cpds.* JP 98310578.

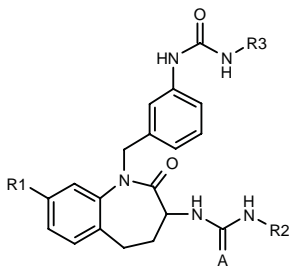
TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

269932

(-)-cis-4-(4-Chlorophenyl)-1-methyl-3-propylpiperidine



C15 H22 Cl N; Mol wt: 251.7988



Compound	R1	R2	R3	A	Formula
270298	H	4-OH-Ph	i-Pr	N(Me)	C ₂₉ H ₃₄ N ₆ O ₃
270299	H	6-benzothiazolyl	i-Pr	O	C ₂₉ H ₃₀ N ₆ O ₃ S
270300	H	4-OH-Ph	i-Pr	NH	C ₂₈ H ₃₂ N ₆ O ₃
270301	H	2-F-Ph	i-Pr	O	C ₂₈ H ₃₀ FN ₆ O ₃
270302	H	6-benzothieryl	i-Pr	O	C ₃₀ H ₃₁ N ₆ O ₃ S
270303	H	6-benzothiazolyl	i-Pr	N(Me)	C ₃₀ H ₃₃ N ₇ O ₂ S
270304	CO ₂ Me	6-benzothieryl	i-Pr	O	C ₃₂ H ₃₃ N ₆ O ₅ S
270305	H	6-benzothieryl	N(Me) ₂	O	C ₂₉ H ₃₀ N ₆ O ₃ S

SOURCE – Shionogi.

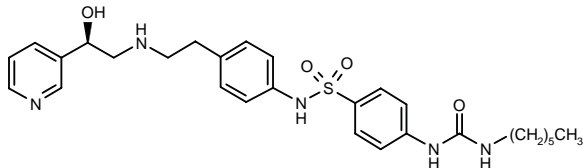
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L-757793

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ACTION – Potent and selective human β_3 -adrenoceptor agonist (EC_{50} = 6.3 nM for adenylyl cyclase activation; 70% activation vs. isoproterenol) with 1300- and 500-fold selectivity over β_1 - and β_2 -adrenoceptors, respectively (IC_{50} = 8000 and 3000 nM, respectively, in binding studies using cloned human receptors). *In vivo* in rhesus monkeys, compound stimulated lipolysis (ED_{50} = 0.2 mg/kg i.v.), with a maximum response equivalent to that elicited by isoproterenol. However, it has poor oral bioavailability and further studies are in progress with the aim of preparing a compound with the biological profile of L-757793 and improved pharmacokinetic properties.

SOURCE – Merck & Co.

REFERENCES

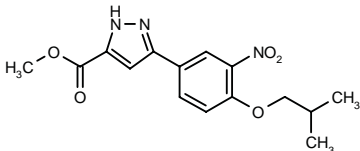
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TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

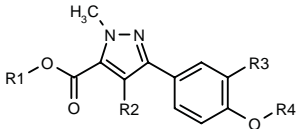
270983

3-(4-Isobutoxy-3-nitrophenyl)-1H-pyrazole-5-carboxylic acid methyl ester



C15 H17 N3 O5; Mol wt: 319.3153

ACTION – Potent xanthine oxidase inhibitor (IC_{50} = 30 nM or less vs. 300 nM for allopurinol) for the treatment of gout and hyperuricemia. Compound is reported to decrease uric acid levels in several animal models. Within this series of 3-phenylpyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
270984	H	H	CN	H	C ₁₂ H ₉ N ₃ O ₃
270985	H	H	CN	(CH ₂) ₃ Ph	C ₂₁ H ₁₉ N ₃ O ₃
270986	i-BuCH ₂	H	NO ₂	i-BuCH ₂	C ₂₁ H ₂₉ N ₃ O ₅
270987	H	H	CN	CH ₂ CH ₂ N(Me) ₂	C ₁₈ H ₁₈ N ₄ O ₃
270988	Me	Cl	CN	t-BuCH ₂	C ₁₈ H ₂₀ ClN ₃ O ₃

SOURCE – Yoshitomi.

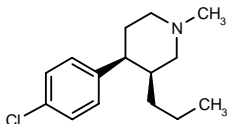
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

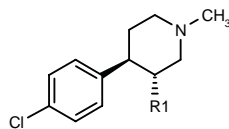
269932

(-)-cis-4-(4-Chlorophenyl)-1-methyl-3-propylpiperidine



C15 H22 Cl N; Mol wt: 251.7988

ACTION – Agent for the treatment of drug addiction, Parkinson's disease or depression, a dopamine reuptake inhibitor ($IC_{50} = 8.3 \pm 0.6$ nM to rat striatal nerve endings) with high affinity for the dopamine transporter site, displacing [3H]-Win-35428 binding from rat striatal membranes with an IC_{50} of 3.0 ± 0.5 nM. Other specifically claimed cocaine analogues include the following:



Compound	R1	Isomer	Formula
269933	CO2Me	trans	C ₁₄ H ₁₈ ClNO ₂
269934	CO2Me	(+)-trans	C ₁₄ H ₁₈ ClNO ₂
269935	Pr	(+)-trans	C ₁₅ H ₂₂ ClN

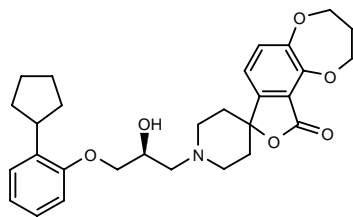
SOURCE – Georgetown University, Washington, D.C. (US).

REFERENCES

1. Kozikowski, A.P. and Araldi, G.L. (Georgetown University) *Analogues of cocaine*. WO 9845263.

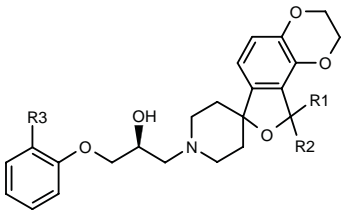
270657

1'-[3-(2-Cyclopentylphenoxy)-2(*S*)-hydroxypropyl]-3,4,8,10-tetrahydro-2*H*-spiro[furo[3,4-*g*][1,5]benzodioxepin-8,4'-piperidin]-10-one



C29 H35 N O6; Mol wt: 493.5965

ACTION – Combined 5-HT_{1A} and 5-HT_{1D} (5-HT_{1Dα}) receptor antagonist with potential in the treatment of a broad range of disorders including nicotine withdrawal symptoms, anxiety, depression, psychosis, hypertension, cognitive disorders, sleep disorders, gastric motility disorders, obesity, eating disorders, cerebrovascular disorders, hyperprolactinemia and sexual dysfunction. Expected to be particularly useful for reducing or eliminating the weight gain that often results from smoking cessation. Within this series of spiro-piperidine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
270658	H	H	SMe	C ₂₄ H ₂₉ NO ₅ S
270659	-O-	-O-	SMe	C ₂₄ H ₂₇ NO ₆ S
270660	H	H	cyclopentyl	C ₂₈ H ₃₅ NO ₅
270661	-O-	-O-	cyclopentyl	C ₂₈ H ₃₃ NO ₆

SOURCE – Lilly.

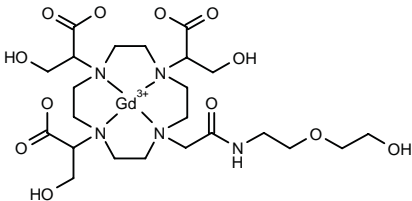
REFERENCES

1. Rocco, V.P. (Eli Lilly and Company) *5-HT_{1A} and 5-HT_{1D} α antagonists*. EP 881224, WO 9853823.

DIAGNOSTIC AGENTS

269852

[2,2',2''-[10-[2-[2-(2-Hydroxyethoxy)ethylamino]-2-oxoethyl]-1,4,7,10-tetrazacyclododecan-1,4,7-triyl]tris(3-hydroxypropanoato)(3-)]gadolinium



C23 H40 Gd N5 O12; Mol wt: 735.842

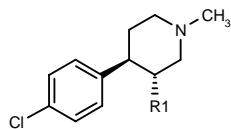
ACTION – Contrast agent for MRI with an extremely favorable neurotoxicity profile in mice ($LD_{50} = 0.23$ mmol/kg i.c.v. vs. 0.064 mmol/kg for Gd-DOTA).

SOURCES – Bracco; Dibra.

REFERENCES

1. Uggeri, F. et al. (Bracco SpA;Dibra SpA) *Chelated complexes of paramagnetic metals with low toxicity*. EP 872479.

ACTION – Agent for the treatment of drug addiction, Parkinson's disease or depression, a dopamine reuptake inhibitor ($IC_{50} = 8.3 \pm 0.6$ nM to rat striatal nerve endings) with high affinity for the dopamine transporter site, displacing [3H]-Win-35428 binding from rat striatal membranes with an IC_{50} of 3.0 ± 0.5 nM. Other specifically claimed cocaine analogues include the following:



Compound	R1	Isomer	Formula
269933	CO2Me	trans	C ₁₄ H ₁₈ ClNO ₂
269934	CO2Me	(+)-trans	C ₁₄ H ₁₈ ClNO ₂
269935	Pr	(+)-trans	C ₁₅ H ₂₂ ClN

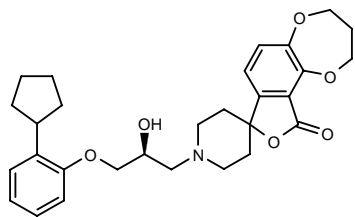
SOURCE – Georgetown University, Washington, D.C. (US).

REFERENCES

1. Kozikowski, A.P. and Araldi, G.L. (Georgetown University) *Analogues of cocaine*. WO 9845263.

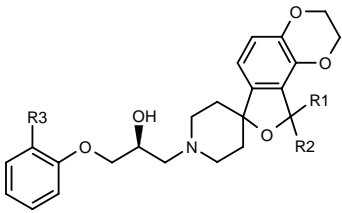
270657

1'-[3-(2-Cyclopentylphenoxy)-2(*S*)-hydroxypropyl]-3,4,8,10-tetrahydro-2*H*-spiro[furo[3,4-*g*][1,5]benzodioxepin-8,4'-piperidin]-10-one



C29 H35 N O6; Mol wt: 493.5965

ACTION – Combined 5-HT_{1A} and 5-HT_{1D} (5-HT_{1Dα}) receptor antagonist with potential in the treatment of a broad range of disorders including nicotine withdrawal symptoms, anxiety, depression, psychosis, hypertension, cognitive disorders, sleep disorders, gastric motility disorders, obesity, eating disorders, cerebrovascular disorders, hyperprolactinemia and sexual dysfunction. Expected to be particularly useful for reducing or eliminating the weight gain that often results from smoking cessation. Within this series of spiro-piperidine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
270658	H	H	SMe	C ₂₄ H ₂₉ NO ₅ S
270659	-O-		SMe	C ₂₄ H ₂₇ NO ₆ S
270660	H	H	cyclopentyl	C ₂₈ H ₃₅ NO ₅
270661	-O-		cyclopentyl	C ₂₈ H ₃₃ NO ₆

SOURCE – Lilly.

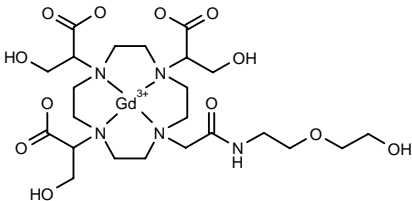
REFERENCES

1. Rocco, V.P. (Eli Lilly and Company) *5-HT_{1A} and 5-HT_{1D} α antagonists*. EP 881224, WO 9853823.

DIAGNOSTIC AGENTS

269852

[2,2',2''-[10-[2-[2-(2-Hydroxyethoxy)ethylamino]-2-oxoethyl]-1,4,7,10-tetrazacyclododecan-1,4,7-triyl]tris(3-hydroxypropanoato)(3-)]gadolinium



C23 H40 Gd N5 O12; Mol wt: 735.842

ACTION – Contrast agent for MRI with an extremely favorable neurotoxicity profile in mice ($LD_{50} = 0.23$ mmol/kg i.c.v. vs. 0.064 mmol/kg for Gd-DOTA).

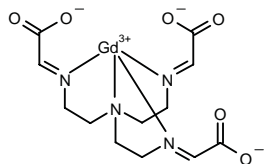
SOURCES – Bracco; Dibra.

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1. Uggeri, F. et al. (Bracco SpA;Dibra SpA) *Chelated complexes of paramagnetic metals with low toxicity*. EP 872479.

270879

[5,5',5"-Nitrilotris[3-aza-2(*E*)-pentenoato](3-)]gadolinium



C₁₂ H₁₅ Gd N₄ O₆; Mol wt: 468.5225

ACTION – Neutral, water-soluble gadolinium complex for use as an MRI contrast agent, reported to possess an increased relaxivity relative to DTPA- and DOTA-based MRI agents.

SOURCE – Nycomed Amersham.

REFERENCES

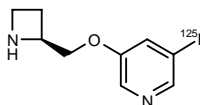
- Schroder, M. and Doble, D.M.J. (Nycomed Amersham plc) *Polydentate imines and their metal complexes*. WO 9839288.

5-[¹²⁵I]-IODO-A-85380

269458

225425 (unlabeled)*

3-[Azetidin-2(*S*)-ylmethoxy]-5-[¹²⁵I]-iodopyridine



C₉ H₁₁ I N₂ O; Mol wt: 288.1989

ACTION – Potent, highly selective neuronal nicotinic acetylcholine (nACh) $\alpha 4\beta 2$ receptor radioligand ($K_i = 11$ pM vs. 34,000 and 250,000 pM, respectively, for the $\alpha 3\beta 4$ and $\alpha 7$ subtypes), proven to be equipotent to but more selective than epibatidine. Compound showed good brain penetration and was able to label mouse nAChRs *in vivo* with high selectivity and specificity. It demonstrated relatively low acute toxicity in mice ($LD_{50} > 3$ mg/kg i.v.). This profile suggests that it may be an excellent SPECT imaging agent for human nACh receptors.

SOURCE – Abbott.

REFERENCES

- Kimes, A.S. et al. *Ex vivo and in vitro autoradiographic analysis of nicotinic acetylcholine receptors (nAChRs) using 5-[¹²⁵I]iodo-A-85380*. Soc Neurosci Abst 1998, 24(Part 1): Abst 40.7.
- Koren, A.O. et al. *Synthesis and evaluation of halogenated analogs of A-85380 as ligands for nicotinic acetylcholine receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 39.9.
- Mukhin, A.G. et al. *5-Iodo-A85380 - A novel highly selective ligand for $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 39.10.
- Musachio, J.L. et al. *5-[I-125/123]iodo-3(2*S*)-azetidylmethoxy]pyridine, a radioiodinated analog of A-85380 for in vivo studies of central nicotinic acetylcholine receptors*. Life Sci 1998, 62(22): PL351.

- Vaupel, D.B. et al. *5-[¹²⁵I]iodo-A-85380: Evaluation as a radiotracer for the in vivo imaging of nicotinic acetylcholine receptors (nAChRs) in the mouse*. Soc Neurosci Abst 1998, 24(Part 1): Abst 40.6.

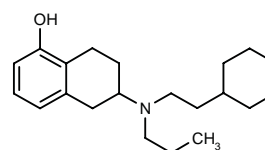
- Vaupel, D.B. et al. *In vivo studies with [¹²⁵I]5-I-A-85380, a nicotinic acetylcholine receptor radioligand*. NeuroReport 1998, 9(10): 2311.

*See **A-84543** Drug Data Report 1995, 017(11): 0983.

ZYY-339

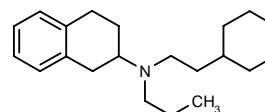
269461

6-[*N*-(2-Cyclohexylethyl)-*N*-propylamino]-5,6,7,8-tetrahydro-1-naphthalenol



C₂₁ H₃₃ N O; Mol wt: 315.4977

ACTION – Potent dopamine D₂ receptor agonist with subnanomolar affinity for high-affinity D₂ sites ($K_i = 0.010$ nM). Compound may be developed as an *in vivo* imaging tracer for PET and radiosynthesis of [¹¹C]-labeled compound is being carried out. Another related compound is:



269462: C₂₁ H₃₃ N

SOURCE – Wright State University, Dayton, OH (US).

REFERENCES

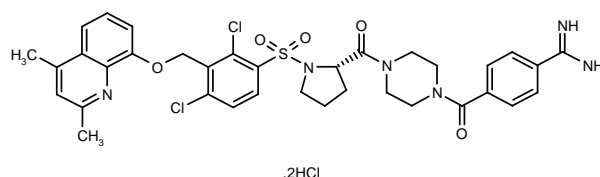
- Mukherjee, J. et al. *Development of dopamine D-2 receptor agonists as potential in vivo imaging agents for PET*. Soc Neurosci Abst 1998, 24(Part 1): Abst 340.2.

PHARMACOLOGICAL TOOLS

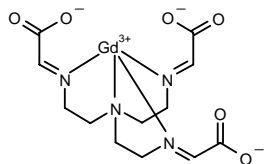
LF-16.0335*

262160

4-[4-[1-[2,4-Dichloro-3-(2,4-dimethylquinolin-8-yloxy-methyl)phenylsulfonyl]pyrrolidin-2(*S*)-ylcarbonyl]-piperazin-1-ylcarbonyl]benzamidinium dihydrochloride



C₃₅ H₃₆ Cl₂ N₆ O₅ S . 2HCl; Mol wt: 796.6002

270879**[5,5',5"-Nitrilotris[3-aza-2(*E*)-pentenoato](3-)]gadolinium**

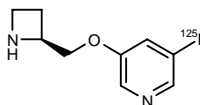
C12 H15 Gd N4 O6; Mol wt: 468.5225

ACTION – Neutral, water-soluble gadolinium complex for use as an MRI contrast agent, reported to possess an increased relaxivity relative to DTPA- and DOTA-based MRI agents.

SOURCE – Nycomed Amersham.

REFERENCES

1. Schroder, M. and Doble, D.M.J. (Nycomed Amersham plc) *Polydentate imines and their metal complexes*. WO 9839288.

5-[¹²⁵I]-IODO-A-85380**269458****225425** (unlabeled)***3-[Azetidin-2(*S*)-ylmethoxy]-5-[¹²⁵I]-iodopyridine**

C9 H11 I N2 O; Mol wt: 288.1989

ACTION – Potent, highly selective neuronal nicotinic acetylcholine (nACh) $\alpha 4\beta 2$ receptor radioligand ($K_i = 11$ pM vs. 34,000 and 250,000 pM, respectively, for the $\alpha 3\beta 4$ and $\alpha 7$ subtypes), proven to be equipotent to but more selective than epibatidine. Compound showed good brain penetration and was able to label mouse nAChRs *in vivo* with high selectivity and specificity. It demonstrated relatively low acute toxicity in mice ($LD_{50} > 3$ mg/kg i.v.). This profile suggests that it may be an excellent SPECT imaging agent for human nACh receptors.

SOURCE – Abbott.

REFERENCES

1. Kimes, A.S. et al. *Ex vivo and in vitro autoradiographic analysis of nicotinic acetylcholine receptors (nAChRs) using 5-[¹²⁵I]iodo-A-85380*. Soc Neurosci Abst 1998, 24(Part 1): Abst 40.7.

2. Koren, A.O. et al. *Synthesis and evaluation of halogenated analogs of A-85380 as ligands for nicotinic acetylcholine receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 39.9.

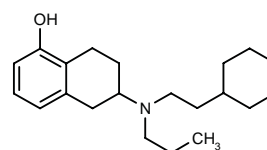
3. Mukhin, A.G. et al. *5-Iodo-A85380 - A novel highly selective ligand for $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 39.10.

4. Musachio, J.L. et al. *5-[I-125/123]iodo-3(2*S*)-azetidylmethoxy)pyridine, a radioiodinated analog of A-85380 for in vivo studies of central nicotinic acetylcholine receptors*. Life Sci 1998, 62(22): PL351.

5. Vaupel, D.B. et al. *5-[¹²⁵I]iodo-A-85380: Evaluation as a radiotracer for the in vivo imaging of nicotinic acetylcholine receptors (nAChRs) in the mouse*. Soc Neurosci Abst 1998, 24(Part 1): Abst 40.6.

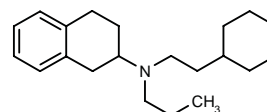
6. Vaupel, D.B. et al. *In vivo studies with [¹²⁵I]5-I-A-85380, a nicotinic acetylcholine receptor radioligand*. NeuroReport 1998, 9(10): 2311.

*See **A-84543** Drug Data Report 1995, 017(11): 0983.

ZYY-339**269461****6-[*N*-(2-Cyclohexylethyl)-*N*-propylamino]-5,6,7,8-tetrahydro-1-naphthalenol**

C21 H33 N O; Mol wt: 315.4977

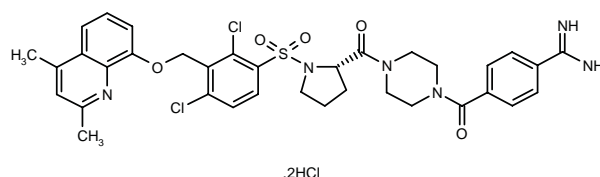
ACTION – Potent dopamine D_2 receptor agonist with subnanomolar affinity for high-affinity D_2 sites ($K_i = 0.010$ nM). Compound may be developed as an *in vivo* imaging tracer for PET and radiosynthesis of [¹¹C]-labeled compound is being carried out. Another related compound is:

**269462:** C21 H33 N

SOURCE – Wright State University, Dayton, OH (US).

REFERENCES

1. Mukherjee, J. et al. *Development of dopamine D-2 receptor agonists as potential in vivo imaging agents for PET*. Soc Neurosci Abst 1998, 24(Part 1): Abst 340.2.

PHARMACOLOGICAL TOOLS**LF-16.0335*****262160****4-[4-[1-[2,4-Dichloro-3-(2,4-dimethylquinolin-8-yloxy-methyl)phenylsulfonyl]pyrrolidin-2(*S*)-ylcarbonyl]-piperazin-1-ylcarbonyl]benzamidinium dihydrochloride**

.2HCl

C35 H36 Cl2 N6 O5 S . 2HCl; Mol wt: 796.6002

ACTION – Potent, selective, nonpeptide human bradykinin B₂ receptor antagonist proven to displace [³H]-bradykinin binding from human B₂ receptors in CHO cells expressing human receptors, INT 407 cells and human umbilical vein with K_i values of 0.84, 1.26 and 2.34 nM, respectively; compound showed high selectivity for B₂ over B₁ receptors and did not interact with other receptors except muscarinic M₁ and M₂ receptors (IC₅₀ = 0.9 and 1 μM, respectively). In functional studies, it inhibited the bradykinin-induced increase in phosphoinositide production (pA₂ = 8.27, 8.28 and 8.21, respectively, for IP1, IP2 and IP3) and it inhibited bradykinin-induced contractions of human umbilical vein (pA₂ = 8.3). Potentially useful as a tool for elucidating the pathophysiological role of human B₂ receptors.

SOURCE – Fournier.

REFERENCES

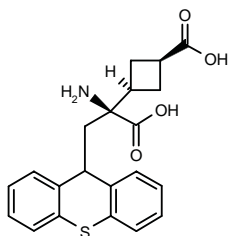
1. Dodey, P. et al. (Laboratoires Fournier SA) *N-Benzenesulphonyl-L-proline derivs. as bradykinin B₂ agonists*. WO 9803503.
2. Pruneau, D. et al. *LF 16.0355, a novel potent and selective nonpeptide antagonist of the human bradykinin B₂ receptor*. Br J Pharmacol 1998, 125(2): 365.

*Identified compound **262160** (see **261542**) Drug Data Report 1998, 020(05): 0382.

LY-393675

267801

2(S)-Amino-2-(*cis*-3-carboxycyclobutyl)-3-(9-thioxanthyl)-propionic acid



C21 H21 N O4 S; Mol wt: 383.4659

ACTION – Group 1 metabotropic glutamate receptor (mGluR) antagonist with IC₅₀s of 0.35 ± 0.08 and 0.48 ± 0.23 μM, respectively, for inhibition of quisqualate-stimulated phosphoinositide hydrolysis in AV-12 cells transfected with mGluR1α and mGluR5a. In mice, compound blocked 3,5-DHPG-induced limbic seizures with an ED₅₀ of 7 mg/kg i.p., whereas it did not block seizures induced by NMDA, AMPA or kainate. The first submicromolar group 1 mGluR antagonist, it is potentially useful as a pharmacological tool for elucidating the physiological role of the mGluRs.

SOURCE – Lilly.

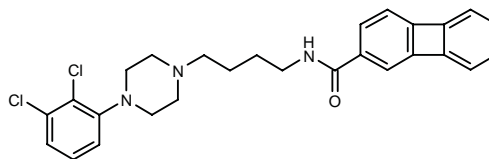
REFERENCES

1. Clark, B.P. and Harris, J.R. (Eli Lilly and Company) *Pharmaceutical acidic cpds*. EP 837061, JP 98120635.
2. Baker, S.R. et al. *LY393675, an alpha-substituted-cyclobutylglycine, is a potent group 1 metabotropic glutamate receptor antagonist*. Soc Neurosci Abst 1998, 24(Part 1): Abst 229.16.
3. Clark, B.P. et al. *α-Substituted-cyclobutylglycine LY393675 potently antagonises group 1 metabotropic glutamate receptors*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.125.

NGB-2849*1,3

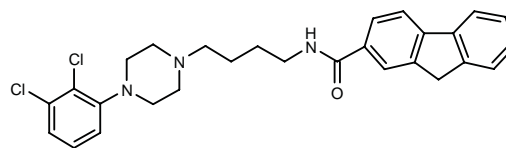
258814

N-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]biphenylene-2-carboxamide



C27 H27 Cl2 N3 O; Mol wt: 480.4363

ACTION – Dopamine D₃ receptor antagonist with high affinity (K_i = 0.9 nM using human receptor) and good selectivity (over 150-fold) over all other dopamine receptor subtypes, α₁-adrenoceptors and 5-HT₂ receptors. In functional studies in D₃-transfected CHO cells, compound antagonized mitogenesis induced by the D₃ agonist quinpirole with an IC₅₀ of 6.8 nM. Potentially useful as a pharmacological tool for elucidating the role of D₃ receptors in human neuropsychiatric disorders such as schizophrenia. Another related compound is:



NGB-2904 [250062],2,3**: C28 H29 Cl2 N3 O

SOURCE – Neurogen.

REFERENCES

1. Chen, X. and Yuan, J. (Neurogen Corp.) *Novel N-aminoalkyl-1-biphenylenyl-2-carboxamides; new dopamine receptor subtype specific ligands*. WO 9738990.
2. Yuan, J. and Chen, X. (Neurogen Corp.) *Novel N-aminoalkylfluorene-carboxamides; a new class of dopamine receptor subtype specific ligands*. EP 873329, JP 98511114, US 5659033, WO 9710229.
3. Yuan, J. et al. *NGB 2904 and NGB 2849: Two highly selective dopamine D3 receptor antagonists*. Bioorg Med Chem Lett 1998, 8(19): 2715.

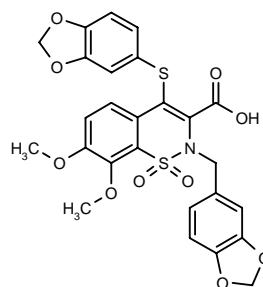
*Identified compound **258814** (see **257251**) Drug Data Report 1998, 020(02): 0114.

Identified compound **250062 Drug Data Report 1997, 019(07): 0596.

PD-164800

269201

2-(1,3-Benzodioxol-5-ylmethyl)-4-(1,3-benzodioxol-5-ylsulfanyl)-7,8-dimethoxy-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide



C26 H21 N O10 S2; Mol wt: 571.5809

ACTION – Nonpeptide endothelin receptor antagonist with good selectivity for ET_A receptors (IC₅₀ = 100 nM for inhibition of [³H]-ET-1 binding in membranes of Ltk- cells expressing the human receptor) over ET_B receptor (IC₅₀ = 4000 nM for inhibition of [³H]-ET-3 binding in membranes of CHO-K1 cells expressing the human receptor). It showed functional ET_A receptor antagonism by inhibiting ET-1-induced arachidonic acid release in cultured rabbit renal vascular smooth muscle cells (IC₅₀ = 150 nM) and by inhibiting ET-1-induced contractions in rabbit femoral artery rings (pA₂ = 5.8). Potentially useful as a tool for elucidating the physiological and pathophysiological role of endothelin.

SOURCE – Warner-Lambert.

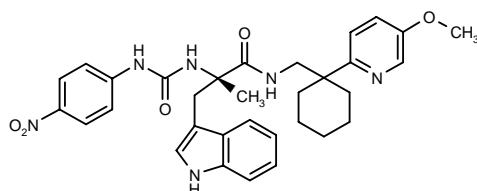
REFERENCES

- Berryman, K.A. et al. (Warner-Lambert Co.) *Benzothiazine dioxides as endothelin antagonists*. EP 811001, WO 9626195.
- Berryman, K.A. et al. *Endothelin receptor antagonists: Synthesis and structure-activity relationships of substituted benzothiazine-1,1-dioxides*. Bioorg Med Chem 1998, 6(9): 1447.

PD-176252

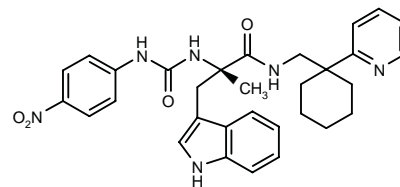
269042

3-(1*H*-Indol-3-yl)-*N*-[1-(5-methoxy-2-pyridinyl)cyclohexylmethyl]-2(*S*)-methyl-2-[3-(4-nitrophenyl)ureido]-propionamide



C32 H36 N6 O5; Mol wt: 584.6734

ACTION – Potent, nonpeptide bombesin BB1 (neuromedin B-preferring) and BB2 (gastrin-releasing peptide) receptor antagonist, with nanomolar affinity for both human BB1 (K_i = 0.17 nM) and BB2 (K_i = 1.0 nM) receptors. In functional assays (bombesin-evoked increases in intracellular Ca²⁺ levels in CHO cells expressing human BB1 and BB2 receptors), compound acted as a competitive antagonist at human BB1 and BB2 receptors, with K_b values of 2.3 and 36 nM, respectively. Another related compound shows selectivity for the BB1 receptor:



PD-168368 [266387]: C31 H34 N6 O4

SOURCE – Warner-Lambert.

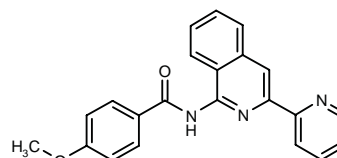
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- Horwell, D.C. and Pritchard, M.C. (Warner-Lambert Co.) *Non-peptide bombesin receptor antagonists*. WO 9807718.
- Ashwood, V. et al. *PD 176252 - The first high affinity non-peptide gastrin-releasing peptide (BB2) receptor antagonist*. Bioorg Med Chem Lett 1998, 8(18): 2589.
- Moody, T.W. *PD168368 is a neuromedin B receptor antagonist for C6 cells*. Soc Neurosci Abstr 1998, 24(Part 1): Abstr 432.5.

VUF-8504

263713

4-Methoxy-*N*-[3-(2-pyridinyl)-1-isoquinolinyl]benzamide



C22 H17 N3 O2; Mol wt: 355.3953

M.p. 161.4-2.9 °C.

ACTION – Potent adenosine A₃ receptor antagonist (K_i = 17 nM against [¹²⁵I]-AB-MECA binding to HEK 293 cells expressing human adenosine A₃ receptors) with high selectivity over A₁ and A₂ receptors. Potentially useful as a pharmacological tool for investigating the physiological role of the human A₃ receptor.

SOURCE – Vrije Universiteit, Amsterdam (NL).

REFERENCES

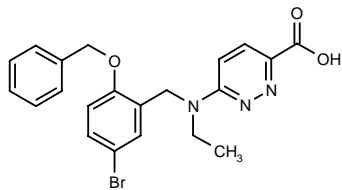
- de Zwart, M.A.H. et al. *Synthesis and copper-dependent antimycoplasmal activity of 1-amino-3-(2-pyridyl)isoquinoline derivatives. 1. Amides*. J Med Chem 1988, 31(4): 716.
- Van Muijlwijk-Koezen, J. et al. *Isoquinoline derivatives as a novel class of adenosine A3 receptor antagonists*. Drug Dev Res 1998, 43(1): Abstr 117.
- van Muijlwijk-Koezen, J.E. et al. *A novel class of adenosine A3 receptor ligands. 2. Structure affinity profile of a series of isoquinoline and quinazoline compounds*. J Med Chem 1998, 41(21): 3994.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

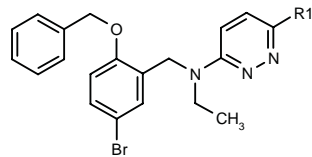
270533

6-[N-[2-(Benzyloxy)-5-bromobenzyl]-N-ethylamino]-3-pyridazinecarboxylic acid



C21 H20 Br N3 O3; Mol wt: 442.3110

ACTION – Analgesic agent structurally different from nonsteroidal antiinflammatory drugs (NSAIDs) and opiates that acts by antagonizing the pain-enhancing effects of E-type prostaglandins by blocking their effects at the EP₁ receptor. Other specifically claimed aromatic amino ether compounds include the following:



Compound	R1	Formula
270534	CONHPr	C ₂₄ H ₂₇ BrN ₄ O ₂
270535	CONHSO ₂ Ph	C ₂₇ H ₂₅ BrN ₄ O ₄ S
270536	3,5-(Me)2-4-isoxazolyl-SO ₂ NHCO	C ₂₆ H ₂₆ BrN ₅ O ₅ S
270538	5-tetrazolyl	C ₂₁ H ₂₀ BrN ₇ O

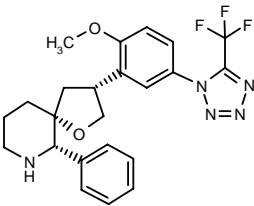
SOURCE – Zeneca.

REFERENCES

1. Breault, G.A. et al. (Zeneca Ltd.) *Aromatic amino ethers as pain relieving agents*. US 5843942, WO 9603380.

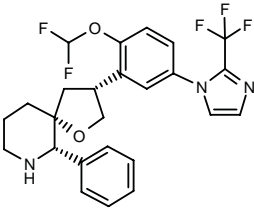
271046

(3*R*,5*R*,6*S*)-3-[2-Methoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]phenyl]-6-phenyl-1-oxa-7-azaspiro-[4.5]decane



C23 H24 F3 N5 O2; Mol wt: 459.4696

ACTION – Agent for the treatment of pain, inflammation, migraine, emesis and postherpetic neuralgia, a tachykinin, especially substance P (NK₁ receptor), antagonist. Another specifically claimed spiro-azacyclic derivative is:



271047: C25 H24 F5 N3 O2

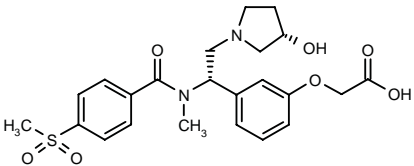
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Curtis, N.R. et al. (Merck Sharp & Dohme Ltd.) *Spiro-azacyclic derivs. and their use as therapeutic agents*. WO 9849170.

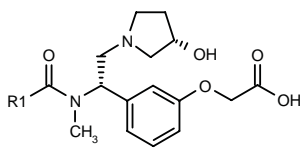
271058

2-[3-[2-[3(*S*)-Hydroxypyrrolidin-1-yl]-1(*S*)-[*N*-methyl-*N*-[4-(methylsulfonyl)benzoyl]amino]ethyl]phenoxy]acetic acid



C23 H28 N2 O7 S; Mol wt: 476.5472

ACTION – κ -Opioid receptor agonist that is reported to be peripherally selective by virtue of its limited ability to cross the blood–brain barrier due to its polarity, thus being devoid of the side effects associated with centrally acting κ agonists. Analgesic activity was demonstrated in the mouse formalin test (ED_{50} = 0.51 mg/kg s.c.), while the absence of central effects was demonstrated in the mouse rotarod test (ED_{50} > 10 mg/kg s.c.). Also claimed for use in the treatment of arthritis, inflammation, migraine, inflammatory disorders of the gastrointestinal tract, inflammatory bowel syndrome and psoriasis. Other specifically claimed compounds within this series of pyrrolidine derivatives include the following:



Compound	R1	Formula
271059	3-benzofuryl	C ₂₄ H ₂₆ N ₂ O ₆
271060	2-benzofuryl	C ₂₄ H ₂₆ N ₂ O ₆
271061	4-benzofuryl-CH ₂	C ₂₅ H ₂₈ N ₂ O ₆

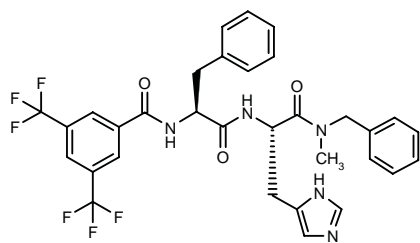
SOURCE – Warner-Lambert.

REFERENCES

1. Horwell, D.C. and Osborne, S. (Warner-Lambert Co.) *Peripherally selective kappa opioid agonists*. WO 9849158.

271435

*N*²-[3,5-Bis(trifluoromethyl)benzoyl]-L-phenylalanyl-L-histidine *N*-benzyl-*N*-methanamide



C32 H29 F6 N5 O3; Mol wt: 645.6011

ACTION – A representative compound from a series of substituted benzamide derivatives with substance P (NK₁ receptor)-antagonist activity.

SOURCE – Asahi Glass.

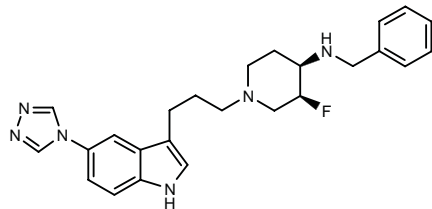
REFERENCES

1. Sakurada, T. et al. (Asahi Glass Co., Ltd.) *Substd. benzamido derivs*. JP 98298197.

ANTIMIGRAINE DRUGS

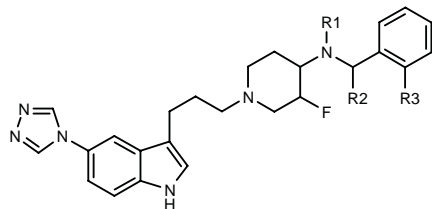
270555

cis-*N*-Benzyl-*N*-[3-fluoro-1-[3-[5-(4*H*-1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propyl]-4-piperidyl]amine



C25 H29 F N6; Mol wt: 432.5441

ACTION – Antimigraine agent, a potent 5-HT_{1D} receptor agonist with at least 10-fold higher affinity for the 5-HT_{1Dα} (5-HT_{1D}) receptor subtype than for 5-HT_{1Dβ} (5-HT_{1B}) receptor subtype, and thus expected to elicit fewer side effects, notably adverse cardiovascular events, than non-subtype-selective 5-HT_{1D} receptor agonists. Other specifically claimed 3-fluoro-4-aminopiperidine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
270556	Me	H	H	cis	C ₂₆ H ₃₁ FN ₆
270557	H	Me	H	trans	C ₂₆ H ₃₁ FN ₆
270558	H	H	CF ₃	trans	C ₂₆ H ₂₈ F ₄ N ₆
270559	Me	H	CF ₃	trans	C ₂₇ H ₃₀ F ₄ N ₆
270560	H	H	CF ₃	cis	C ₂₆ H ₂₈ F ₄ N ₆
270561	Me	H	CF ₃	cis	C ₂₇ H ₃₀ F ₄ N ₆

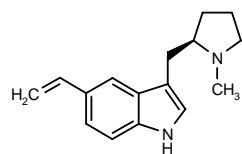
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. and Russell, M.G. (Merck Sharp & Dohme Ltd.) *3-Fluoro-4-aminopiperidine derivs. as 5-HT receptor agonists*. US 5837715.

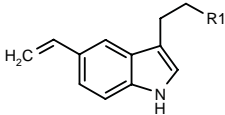
271350

3-[1-Methylpyrrolidin-2(*R*)-ylmethyl]-5-vinyl-1*H*-indole



C16 H20 N2; Mol wt: 240.3480

ACTION – Antimigraine agent, a selective 5-HT_{1D}-like receptor agonist with an EC₅₀ value of 0.08 µM in the isolated rabbit saphenous vein assay compared to a value of 0.22 µM for sumatriptan. Other specifically claimed compounds from this series of 5-alkenyl or 5-alkynyl indole derivatives include the following:



Compound	R1	Formula
271351	N(Me)2	C ₁₄ H ₁₈ N ₂
271352	1-pyrrolidinyl	C ₁₆ H ₂₀ N ₂
271353	1-Me-3-pyrrolidinyl	C ₁₇ H ₂₂ N ₂

SOURCE – Allelix Biopharmaceuticals.

REFERENCES

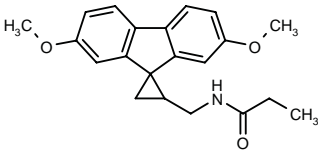
1. Meng, Q. et al. (Allelix Biopharmaceuticals Inc.) *5-Alkenyl and 5-alkynyl indole cpds.* US 5856510.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

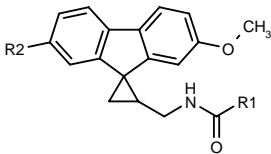
271330

N-[2',7'-Dimethoxyspiro[cyclopropane-1,9'-fluoren]-2-ylmethyl]propionamide



C₂₁ H₂₃ N O₃; Mol wt: 337.4167

ACTION – Agent for the treatment of sleep disorders, a melatonin agonist proven to inhibit [¹²⁵I]-iodomelatonin binding to human mt₁ (ML_{1A}) receptors expressed in NIH3T3 cells with an IC₅₀ value of < 10 nM. A representative compound from a series of specifically claimed spirocyclopropyl fluorenyl derivatives, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
271331	Et	OMe	(-)	C ₂₁ H ₂₃ NO ₃
271332	Et	OMe	(+)	C ₂₁ H ₂₃ NO ₃
271333	Me	OMe		C ₂₀ H ₂₁ NO ₃
271334	Pr	OMe		C ₂₂ H ₂₅ NO ₃
271335	cyclopropyl	OMe		C ₂₂ H ₂₃ NO ₃
271336	Et	F	cis	C ₂₀ H ₂₀ FNO ₂
271337	Et	F	trans	C ₂₀ H ₂₀ FNO ₂

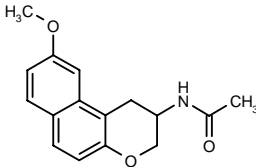
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. LeBoulluec, K.L. and Takaki, K.S. (Bristol-Myers Squibb Co.) *Spirocyclopropyl fluorenes as melatonergic agents.* WO 9852554.

272172

N-(9-Methoxy-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-2-yl)acetamide



C₁₆ H₁₇ N O₃; Mol wt: 271.3143

ACTION – Agent with high affinity for melatonin receptors, a representative compound from a series of substituted heterocyclic derivatives potentially useful for the treatment of sleep disorders, seasonal depression, cardiovascular disorders, circadian rhythm disorders, appetite disorders and obesity.

SOURCE – ADIR.

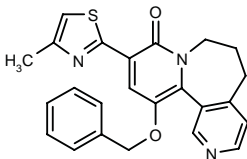
REFERENCES

1. Guillaumet, G. et al. (ADIR et Cie.) *Substd. heterocyclic cpds., method for preparing and compsns. containing same.* WO 9852935.

ANXIOLYTICS

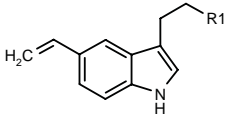
271527

12-(Benzyloxy)-10-(4-methylthiazol-2-yl)-5,6,7,9-tetrahydrodiprido[1,2-*a*:3,4-*c*]azepin-9-one



C₂₄ H₂₁ N₃ O₂ S; Mol wt: 415.5149

ACTION – Antimigraine agent, a selective 5-HT_{1D}-like receptor agonist with an EC₅₀ value of 0.08 µM in the isolated rabbit saphenous vein assay compared to a value of 0.22 µM for sumatriptan. Other specifically claimed compounds from this series of 5-alkenyl or 5-alkynyl indole derivatives include the following:



Compound	R1	Formula
271351	N(Me)2	C ₁₄ H ₁₈ N ₂
271352	1-pyrrolidinyl	C ₁₆ H ₂₀ N ₂
271353	1-Me-3-pyrrolidinyl	C ₁₇ H ₂₂ N ₂

SOURCE – Allelix Biopharmaceuticals.

REFERENCES

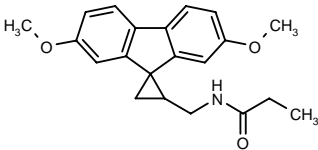
1. Meng, Q. et al. (Allelix Biopharmaceuticals Inc.) *5-Alkenyl and 5-alkynyl indole cpds.* US 5856510.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

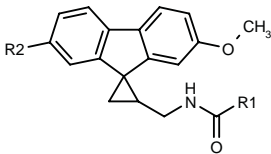
271330

N-[2',7'-Dimethoxyspiro[cyclopropane-1,9'-fluoren]-2-ylmethyl]propionamide



C₂₁ H₂₃ N O₃; Mol wt: 337.4167

ACTION – Agent for the treatment of sleep disorders, a melatonin agonist proven to inhibit [¹²⁵I]-iodomelatonin binding to human mt₁ (ML_{1A}) receptors expressed in NIH3T3 cells with an IC₅₀ value of < 10 nM. A representative compound from a series of specifically claimed spirocyclopropyl fluorenyl derivatives, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
271331	Et	OMe	(-)	C ₂₁ H ₂₃ NO ₃
271332	Et	OMe	(+)	C ₂₁ H ₂₃ NO ₃
271333	Me	OMe		C ₂₀ H ₂₁ NO ₃
271334	Pr	OMe		C ₂₂ H ₂₅ NO ₃
271335	cyclopropyl	OMe		C ₂₂ H ₂₃ NO ₃
271336	Et	F	cis	C ₂₀ H ₂₀ FNO ₂
271337	Et	F	trans	C ₂₀ H ₂₀ FNO ₂

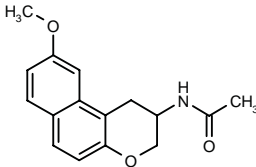
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. LeBoulluec, K.L. and Takaki, K.S. (Bristol-Myers Squibb Co.) *Spirocyclopropyl fluorenes as melatonergic agents.* WO 9852554.

272172

N-(9-Methoxy-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-2-yl)acetamide



C₁₆ H₁₇ N O₃; Mol wt: 271.3143

ACTION – Agent with high affinity for melatonin receptors, a representative compound from a series of substituted heterocyclic derivatives potentially useful for the treatment of sleep disorders, seasonal depression, cardiovascular disorders, circadian rhythm disorders, appetite disorders and obesity.

SOURCE – ADIR.

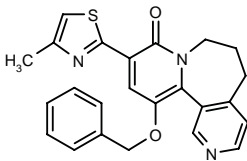
REFERENCES

1. Guillaumet, G. et al. (ADIR et Cie.) *Substd. heterocyclic cpds., method for preparing and compsns. containing same.* WO 9852935.

ANXIOLYTICS

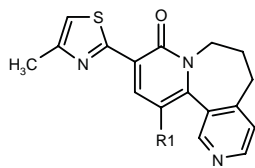
271527

12-(Benzyloxy)-10-(4-methylthiazol-2-yl)-5,6,7,9-tetrahydrodiprido[1,2-*a*:3,4-*c*]azepin-9-one



C₂₄ H₂₁ N₃ O₂ S; Mol wt: 415.5149

ACTION – Agent for the treatment of CNS disorders such as anxiety, epilepsy, depression, migraine, psychoses, neurodegenerative disorders and circadian rhythm disorders with high affinity for the GABA_A α2 and/or α3 subunit. Other specifically claimed compounds within this series of tricyclic pyridone derivatives include the following:



Compound	R1	Formula
271528	3-Cl-4-MeO-Ph	C ₂₄ H ₂₀ ClN ₃ O ₂ S
271529	4-CHO-Ph	C ₂₄ H ₁₉ N ₃ O ₂ S
271531	Ph-ethynylene	C ₂₅ H ₁₉ N ₃ OS
271532	1,3-benzodioxol-5-yl	C ₂₄ H ₁₉ N ₃ O ₃ S
271533	2,5-(MeO)2-Ph	C ₂₅ H ₂₃ N ₃ O ₃ S
271534	2-benzofuryl	C ₂₅ H ₁₉ N ₃ O ₂ S
271535	2,4-(Cl)2-Ph	C ₂₃ H ₁₇ Cl ₂ N ₃ OS

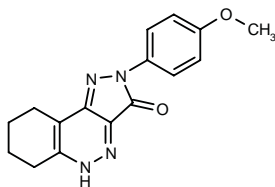
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Harrison, T. et al. (Merck Sharp & Dohme Ltd.) *Tricyclic pyridone analogues as GABA-A receptor ligands*. WO 9850384.

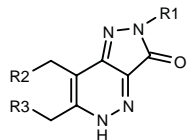
271831

2-(4-Methoxyphenyl)-3,5,6,7,8,9-hexahydro-2H-pyrazolo[4,3-c]cinnolin-3-one



C16 H16 N4 O2; Mol wt: 296.3284

ACTION – Agent for the treatment or prevention of CNS disorders, particularly anxiety and convulsions, with high affinity for the α2 and/or α3 subunit of the human GABA_A receptor (K_i = 100 nM or less for displacement of [³H]-flumazenil binding to human receptors). Other specifically claimed compounds within this series of tricyclic pyrazolo-pyridazinone derivatives include the following:



Compound	R1	R2,R3	Formula
271832	2-Pyr	-(CH2)2-	C ₁₄ H ₁₃ N ₅ O
271833	3,4-(Me)2-Ph	-(CH2)2-	C ₁₇ H ₁₈ N ₄ O
271834	4-EtO-Ph	-(CH2)2-	C ₁₇ H ₁₈ N ₄ O ₂
271835	4-MeO-Ph	-(CH2)3-	C ₁₇ H ₁₈ N ₄ O ₂
271836	4-F-Ph	-(CH2)3-	C ₁₆ H ₁₅ FN ₄ O
271837	4-Me-2-Pyr	-(CH2)3-	C ₁₆ H ₁₇ N ₅ O

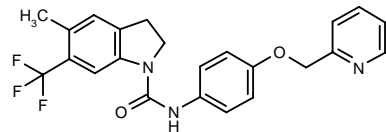
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Blurton, P. and Fletcher, S.R. (Merck Sharp & Dohme Ltd.) *Tricyclic pyrazolo-pyridazinone analogues as GABA-A receptor ligands*. WO 9900391.

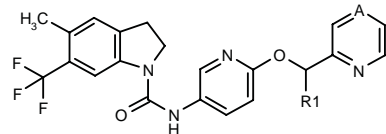
272168

5-Methyl-N-[4-(2-pyridinylmethoxy)phenyl]-6-(trifluoromethyl)indoline-1-carboxamide



C23 H20 F3 N3 O2; Mol wt: 427.4240

ACTION – 5-HT_{2C} receptor antagonist with potential in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive–compulsive disorder, migraine, Alzheimer’s disease, sleep disorders, eating disorders, panic attacks, drug withdrawal symptoms, schizophrenia and disorders associated with spinal trauma and/or head injury. Compound is also expected to be useful in the treatment of glaucoma, certain gastrointestinal disorders such as irritable bowel syndrome, as well as microvascular diseases such as macular edema and retinopathy. Other specifically claimed compounds within this series of indoline derivatives include the following:



Compound	R1	A	Formula
272169	H	N	C ₂₁ H ₁₈ F ₃ N ₅ O ₂
272608	Me	CH	C ₂₃ H ₂₁ F ₃ N ₄ O ₂

SOURCE – SmithKline Beecham.

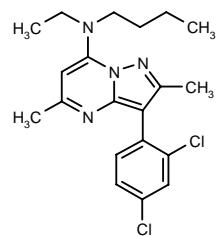
REFERENCES

1. Bromidge, S.M. (SmithKline Beecham plc) *Indoline derivs. as 5HT_{2C} receptor antagonists*. WO 9852943.

PD-171729¹⁻³

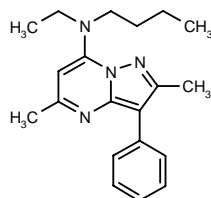
267912

N-Butyl-N-[3-(2,4-dichlorophenyl)-2,5-dimethylpyrazolo-[1,5-a]pyrimidin-7-yl]-N-ethylamine



C20 H24 Cl2 N4; Mol wt: 391.3436

ACTION – Potent and selective corticotropin-releasing factor CRF₁ receptor antagonist ($K_i = 5$ nM using cloned human receptors) proven to dose-dependently (5-20 mg/kg p.o.) attenuate the elevation in norepinephrine and MHPG levels in rat medial prefrontal cortex induced by i.c.v. infusion of recombinant human CRF(1-41). Potentially useful for the treatment of diseases involving CRF secretion such as anxiety, depression and inflammatory disorders. Another related pyrazolo-[1,5-a]pyrimidine CRF₁ antagonist is:



269635³: C20 H26 N4

SOURCE – Warner-Lambert.

REFERENCES

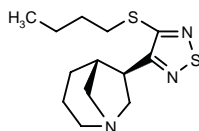
- Davis, M.D. and Cooke, L.W. *The non-peptide CRF-R1 antagonist, PD171729, inhibits corticotropin releasing factor (CRF)-induced norepinephrine release in the cortex of rats.* Soc Neurosci Abst 1998, 24(Part 2): Abst 583.2.
- Pugsley, T. et al. *In vitro and in vivo characterization of PD 171729, a nonpeptide corticotrophin releasing factor (CRF) receptor antagonist.* Soc Neurosci Abst 1998, 24(Part 1): Abst 234.10.
- Wustrow, D.J. et al. *Pyrazolo[1,5-a]pyrimidine CRF-1 receptor antagonists.* Bioorg Med Chem Lett 1998, 8(16): 2067.

ANTIPSYCHOTIC DRUGS

269898¹⁻⁶

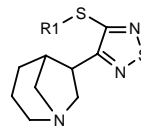
183592⁺ (as *exo*-isomer)

(5*R*,6*R*)-3-(1-Azabicyclo[3.2.1]oct-6-yl)-4-(butylsulfanyl)-1,2,5-thiadiazole



C13 H21 N3 S2; Mol wt: 283.4619

ACTION – Antipsychotic agent, a muscarinic agonist with high affinity for M₂ and M₄ muscarinic receptor subtypes ($K_i = 0.50$ nM against [³H]-oxotremorine-M in rat brain homogenates). *In vivo*, compound exhibited an antipsychotic profile, as demonstrated by inhibition of apomorphine-induced climbing in mice (ED₅₀ = 0.012 mg/kg s.c.) and of conditioned avoidance responding in rats (ED₅₀ = 0.017 mg/kg s.c.). It is devoid of undesirable cholinergic side effects (ED₅₀ > 3 mg/kg s.c. for induction of salivation and tremor in mice) and it did not induce catalepsy. Other 1,2,5-thiadiazole analogues with a similar profile of activity are:



Compound	R1	Isomer	Formula
269897¹⁻⁶	Bu	(5 <i>S</i> ,6 <i>S</i> - <i>exo</i>)	C ₁₃ H ₂₁ N ₃ S ₂
269899^{1-4,6}	Pr	(5 <i>R</i> ,6 <i>R</i> - <i>exo</i>)	C ₁₂ H ₁₉ N ₃ S ₂
269900^{1-4,6}	Pr	(5 <i>S</i> ,6 <i>S</i> - <i>exo</i>)	C ₁₂ H ₁₉ N ₃ S ₂

SOURCES – Lilly; Novo Nordisk.

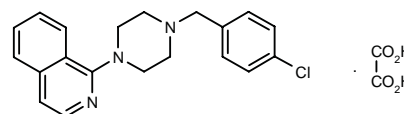
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- Bymaster, F.P. et al. (Eli Lilly and Company) *Transdermal formulation of a cpd. having muscarinic activity.* EP 727208.
- Sauerberg, P. and Olesen, P.H. (Novo Nordisk A/S) *Heterocyclic cpds. and their preparation and use.* EP 544779, JP 94500542, US 5260314, US 5418240, US 5527813, US 5578602, WO 9203433.
- Mitch, C.H. et al. *Muscarinic analgesics with potent and selective effects on the gastrointestinal tract: Potential application for the treatment of irritable bowel syndrome.* J Med Chem 1997, 40(4): 538.
- Sauerberg, P. et al. *Muscarinic agonists with antipsychotic-like activity: Structure-activity relationships of 1,2,5-thiadiazole analogues with functional dopamine antagonist activity.* J Med Chem 1998, 41(22): 4378.

*Drug Data Report 1992, 014(08): 0681.

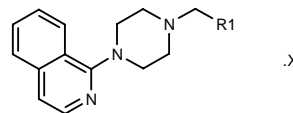
271082

1-[4-(4-Chlorobenzyl)piperazin-1-yl]isoquinoline oxalate



C20 H20 Cl N3 . C2 H2 O4; Mol wt: 427.8858

ACTION – Antipsychotic agent with high affinity and selectivity for dopamine D₄ receptors ($K_i = 5$ nM) relative to D₂ receptors ($K_i = 556$ nM). Within this series of 1-(isoquinolin-1-yl)-4-(1-phenylmethyl)piperazines, the following are also specifically claimed:



Compound	R1	X	Formula
271083	3,5-(F)2-Ph	oxalate	C ₂₀ H ₁₉ F ₂ N ₃ ·C ₂ H ₂ O ₄
271084	3,4-(F)2-Ph	oxalate	C ₂₀ H ₁₉ F ₂ N ₃ ·C ₂ H ₂ O ₄
271085	2-Naph	HCl	C ₂₄ H ₂₃ N ₃ ·HCl
271086	3-Cl-Ph		C ₂₀ H ₂₀ ClN ₃
271087	4-Me-Ph	oxalate	C ₂₁ H ₂₃ N ₃ ·C ₂ H ₂ O ₄
271088	1,3-benzodioxol-5-yl	HCl	C ₂₁ H ₂₁ N ₃ O ₂ ·HCl

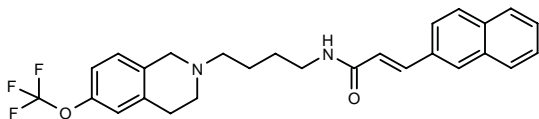
SOURCE – Neurogen.

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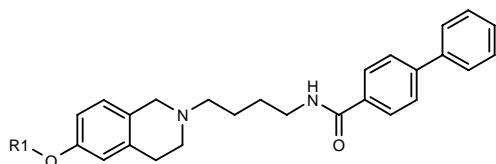
271101

3-(2-Naphthyl)-N-[4-[6-(trifluoromethoxy)-1,2,3,4-tetrahydro-2-isoquinolinyl]butyl]-2(*E*)-propenamide



C₂₇ H₂₇ F₃ N₂ O₂; Mol wt: 468.5163

ACTION – Antipsychotic agent with affinity for dopamine D₃ receptors, as demonstrated in binding and functional experiments. Within this series of specifically claimed tetrahydro isoquinolines, the following are also included:



Compound	R1	Formula
271102	Me	C ₂₇ H ₃₀ N ₂ O ₂
271103	H	C ₂₆ H ₂₈ N ₂ O ₂
271104	SO ₂ CF ₃	C ₂₇ H ₂₇ F ₃ N ₂ O ₄ S

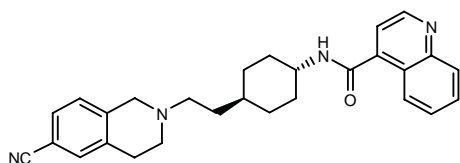
SOURCE – SmithKline Beecham.

REFERENCES

1. Johns, A. et al. (SmithKline Beecham plc) *Substd. tetrahydro isoquinolines as modulators of dopamine D3 receptors*. WO 9850363.

271105

trans-N-[4-[2-(6-Cyano-1,2,3,4-tetrahydro-2-isoquinoliny)ethyl]cyclohexyl]quinoline-4-carboxamide



C₂₈ H₃₀ N₄ O; Mol wt: 438.5720

ACTION – Antipsychotic agent with affinity for dopamine D₃ receptors, as demonstrated in binding and functional experiments. A representative compound within a series of specifically claimed tetrahydroisoquinoline derivatives.

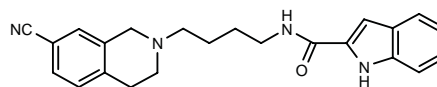
SOURCE – SmithKline Beecham.

REFERENCES

1. Branch, C.L. et al. (SmithKline Beecham plc) *Tetrahydroisoquinoline derivs. as modulators of dopamine D3 receptors*. WO 9850364.

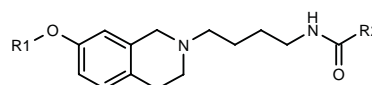
271113

N-[4-(7-Cyano-1,2,3,4-tetrahydro-2-isoquinolinyl)butyl]-1*H*-indole-2-carboxamide



C₂₃ H₂₄ N₄ O; Mol wt: 372.4696

ACTION – Antipsychotic agent with higher affinity for dopamine D₃ receptors as compared to D₂ receptors; it was reported to have a pK_i value of 7.0-8.5 in binding experiments using cloned human D₃ receptors. Other specifically claimed substituted tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	Formula
271114	CF ₃	2-indolyl	C ₂₃ H ₂₄ F ₃ N ₃ O ₂
271115	SO ₂ CF ₃	5-indolyl	C ₂₃ H ₂₄ F ₃ N ₃ O ₄ S
271116	SO ₂ CF ₃	2-indolyl	C ₂₃ H ₂₄ F ₃ N ₃ O ₄ S
271117	CF ₃	5-MeO-2-indolyl	C ₂₄ H ₂₆ F ₃ N ₃ O ₃
271118	CF ₃	2-benzothieryl	C ₂₃ H ₂₄ F ₃ N ₂ O ₂ S
271119	CF ₃	5-Cl-2-indolyl	C ₂₃ H ₂₃ ClF ₃ N ₃ O ₂
271120	CF ₃	5-Me-2-indolyl	C ₂₄ H ₂₆ F ₃ N ₃ O ₂
271121	CF ₃	5-F-2-indolyl	C ₂₃ H ₂₃ F ₄ N ₃ O ₂

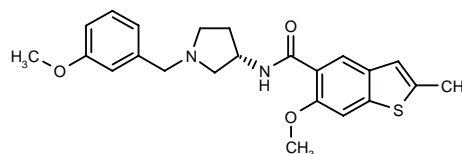
SOURCE – SmithKline Beecham.

REFERENCES

1. Branch, C.L. and Stemp, G. (SmithKline Beecham plc) *Substd. tetrahydro-isoquinoline derivs. as modulators of dopamine D3 receptors*. WO 9849145.

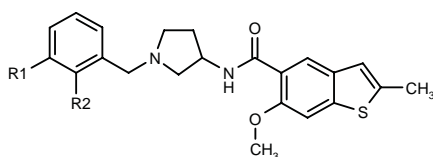
271407

6-Methoxy-N-[1-(3-methoxybenzyl)pyrrolidin-3(*S*)-yl]-2-methyl[1]benzothiophene-5-carboxamide



C₂₃ H₂₆ N₂ O₃ S; Mol wt: 410.5354

ACTION – Antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding studies by K_i values of 0.63 and 22,000 nM for dopamine D₄ and D₂ receptors, respectively. Other related compounds include the following:



Compound	R1	R2	Formula
271408	H	Cl	C ₂₂ H ₂₃ ClN ₂ O ₂ S
271409	Cl	H	C ₂₂ H ₂₃ ClN ₂ O ₂ S

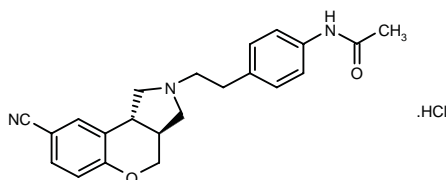
SOURCE – Shionogi.

REFERENCES

1. Takada, S. et al. (Shionogi & Co. Ltd.) *Cpds. having dopamine receptor antagonism*. JP 98298180.

271411

N-[4-[2-[(3 α ,9 β)-8-Cyano-2,3,3a,4,9b-hexahydro-1*H*-[1]benzopyrano[3,4-*c*]pyrrol-2-yl]ethyl]phenyl]acetamide hydrochloride



C₂₂ H₂₃ N₃ O₂ . HCl; Mol wt: 397.9036

ACTION – Antipsychotic agent with high affinity for dopamine D₃ receptors and selectivity over dopamine D₂ receptors, and thus expected to possess a low liability for extrapyramidal side effects. A specifically claimed compound within a series of chromene derivatives.

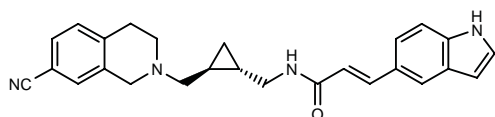
SOURCE – ADIR.

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1. Lavielle, G. et al. (ADIR et Cie.) *Chromene derivs., process for their preparation and pharmaceutical compns. containing them*. EP 887350.

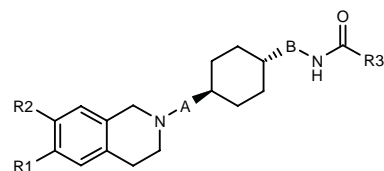
271416

trans-*N*-[2-(7-Cyano-1,2,3,4-tetrahydro-2-isoquinolinylmethyl)cyclopropylmethyl]-3-(1*H*-indol-5-yl)-2(*E*)-propanamide



C₂₆ H₂₆ N₄ O; Mol wt: 410.5184

ACTION – Antipsychotic agent that exhibits selective affinity for dopamine D₃ receptors relative to D₂ receptors and is thus expected to be devoid of extrapyramidal side effects. Other specifically claimed compounds within this series of substituted tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	R3	A	B	Formula
271417	CN	H	4-F-PhCH=CH	bond	bond	C ₂₅ H ₂₆ FN ₃ O
271418	H	CN	CH=CHPh	bond	bond	C ₂₅ H ₂₇ N ₃ O
271419	H	CN	2-indolyl	bond	CH ₂ CH ₂	C ₂₇ H ₃₀ N ₄ O
271420	H	CN	CH=CHPh	CH ₂	CH ₂	C ₂₇ H ₃₁ N ₃ O
271421	H	CN	2-indolyl	CH ₂	CH ₂	C ₂₇ H ₃₀ N ₄ O

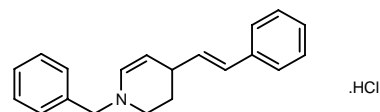
SOURCE – SmithKline Beecham.

REFERENCES

1. Johnson, C.N. and Stemp, G. (SmithKline Beecham plc) *Substd. tetrahydro-isoquinoline derivs. as modulators of dopamine D3 receptors*. WO 9851671.

271739

1-Benzyl-4-[2(*E*)-phenylvinyl]-1,2,3,4-tetrahydropyridine hydrochloride



C₂₀ H₂₁ N . HCl; Mol wt: 311.8538

ACTION – Agent with high affinity for dopamine D₄ receptors (K_i < 1.5 μ M for displacement of [³H]-spiperone binding to human D₄ receptors expressed in clonal cells), potentially useful for the treatment or prevention of schizophrenia, depression, anxiety, nausea, Parkinson's disease and extrapyramidal side effects associated with conventional neuroleptic agents. A representative compound within a series of tetrahydropyridine derivatives.

SOURCE – Merck Sharp & Dohme.

REFERENCES

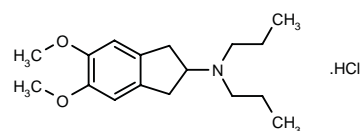
1. Curtis, N.R. et al. (Merck Sharp & Dohme Ltd.) *Tetrahydropyridine derivs. as dopamine receptor subtype ligands*. US 5861407.

PNU-99194A

269259

5,6-Dimethoxy-*N,N*-dipropyl-2,3-dihydro-1*H*-inden-2-amine hydrochloride

U-99194A



C₁₇ H₂₇ N O₂ . HCl; Mol wt: 313.8662

White crystals, m.p. 210-4 °C.

ACTION – Potential antischizophrenic agent, a dopamine antagonist with high affinity for D_3 receptors ($K_i = 78$ nM for displacement of [3H]-spiperone binding from cloned rat D_3 receptors) and selectivity over D_2 receptors ($K_i = 1572$ nM for displacement of [3H]-PNU-86170 binding from rat cloned D_2 receptors); compound was inactive at acetylcholine, histamine and other monoaminergic receptors and uptake sites. *In vivo* experiments indicated that compound produced behavioral activation without sedation or catalepsy, this profile being different from that of D_2 -preferring antagonists such as haloperidol. Its profile suggests antipsychotic-like activity with particular efficacy against negative symptoms and cognitive deficits, and a lack of extrapyramidal side effects.

SOURCE – Pharmacia & Upjohn.

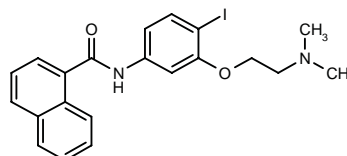
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ANTIDEPRESSANTS

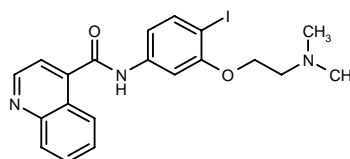
271096

N-[3-[2-(Dimethylamino)ethoxy]-4-iodophenyl]naphthalene-1-carboxamide



C21 H21 I N2 O2; Mol wt: 460.3089

ACTION – Relatively fast-acting antidepressant with combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor-antagonist activity. Also potentially useful in the treatment of other CNS disorders such as anxiety, obsessive-compulsive disorder, memory, eating, sleep and motor disorders. Another specifically claimed urea derivative is:



271097: C20 H20 I N3 O2

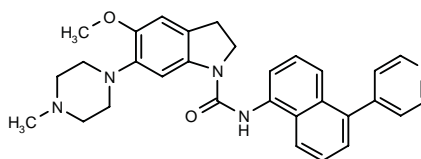
SOURCE – SmithKline Beecham.

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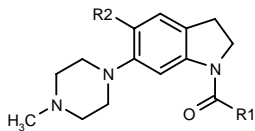
271106

5-Methoxy-6-(4-methyl-1-piperazinyl)-*N*-[5-(4-pyridinyl)-1-naphthyl]-1-indolinecarboxamide



C30 H31 N5 O2; Mol wt: 493.6079

ACTION – Relatively fast-acting antidepressant with combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor-antagonist activity ($pK_i > 8.0$). Also potentially useful for other CNS disorders such as anxiety, obsessive-compulsive disorder, memory, eating, sleep and motor disorders. Within this series of specifically claimed indole derivatives, the following are also included:



Compound	R1	R2	Formula
271107	4-(4-Pyr)-1-Naph-NH	Cl	C ₂₉ H ₂₈ ClN ₅ O
271108	4-(4-Pyr)-1-Naph-NH	vinyl	C ₃₁ H ₃₁ N ₅ O
271109	5-(4-Pyr)-1-Naph-CH2	OMe	C ₃₁ H ₃₂ N ₄ O ₂
271110	5-(4-Pyr)-1-Naph-CH2	Cl	C ₃₀ H ₂₈ ClN ₄ O
271111	4-[2,6-(Me)2-4-Pyr]-PhNH	Br	C ₂₇ H ₃₀ BrN ₅ O
271112	4-(8-quinolyl)-PhNH	Cl	C ₂₉ H ₂₈ ClN ₅ O

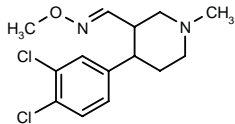
SOURCE – SmithKline Beecham.

REFERENCES

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271374

4-(3,4-Dichlorophenyl)-1-methyl-3-piperidinecarbaldehyde *O*-methyloxime



C14 H18 Cl2 N2 O; Mol wt: 301.2152

ACTION – Agent for the treatment of CNS disorders including depression, Parkinson’s disease, cognitive disorders and obesity, a specifically claimed compound within a series of piperidine derivatives proven to inhibit the reuptake of the neurotransmitters dopamine, norepinephrine and 5-HT with IC₅₀ values of 0.024, 0.014 and 0.12 nM, respectively.

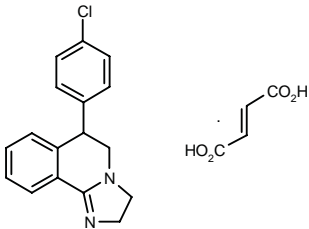
SOURCE – NeuroSearch.

REFERENCES

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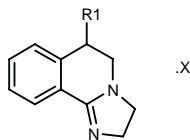
271442

(+)-6-(4-Chlorophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*a*]-isoquinoline fumarate



C17 H15 Cl N2 . C4 H4 O4; Mol wt: 398.8441

ACTION – Antidepressant, a dopamine, norepinephrine and 5-HT reuptake inhibitor (pK_i = 7.2, 8.15 and 7.0, respectively). Other specifically claimed tetrahydroimidazo[2,1-*a*]isoquinoline derivatives include the following:



Compound	R1	X	Isomer	Formula
271443	4-F-Ph	maleate		C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271444	4-Cl-Ph	fumarate	(-)	C ₁₇ H ₁₅ ClN ₂ .C ₄ H ₄ O ₄
271445	4-Me-Ph	maleate		C ₁₈ H ₁₈ N ₂ .C ₄ H ₄ O ₄
271446	4-F-Ph	fumarate	(+)	C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271447	4-F-Ph	fumarate	(-)	C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271448	2-Naph	fumarate		C ₂₁ H ₁₈ N ₂ .C ₄ H ₄ O ₄

SOURCE – Akzo Nobel.

REFERENCES

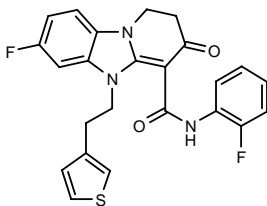
1. Leysen, D. and Ruigt, G.S.F. (Akzo Nobel N.V.) *Tetrahydroimidazo(2,1-a)isoquinoline derivs.* EP 887349.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

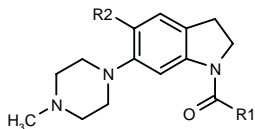
271826

7-Fluoro-*N*-(2-fluorophenyl)-3-oxo-5-[2-(3-thienyl)ethyl]-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole-4-carboxamide



C24 H19 F2 N3 O2 S; Mol wt: 451.4951

ACTION – Agent with high affinity for the benzodiazepine binding site on GABA_A receptors, as demonstrated in a binding assay using [³H]-flunitrazepam as the radioligand (IC₅₀ = 0.096 nM), with potential as a muscle relaxant, sedative, anxiolytic, anticonvulsant and antiepileptic agent and for managing alcoholism and drug overdose. Anticonvulsant activity was demonstrated by inhibition of pentylenetetrazol-induced convulsions in mice (ED₅₀ = 0.1 mg/kg i.p.). Compound also exhibited anxiolytic activity in a rat conflict test. Other specifically claimed compounds within this series of 3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole-4-carboxamide derivatives include the following:



Compound	R1	R2	Formula
271107	4-(4-Pyr)-1-Naph-NH	Cl	C ₂₉ H ₂₈ ClN ₅ O
271108	4-(4-Pyr)-1-Naph-NH	vinyl	C ₃₁ H ₃₁ N ₅ O
271109	5-(4-Pyr)-1-Naph-CH2	OMe	C ₃₁ H ₃₂ N ₄ O ₂
271110	5-(4-Pyr)-1-Naph-CH2	Cl	C ₃₀ H ₂₈ ClN ₄ O
271111	4-[2,6-(Me)2-4-Pyr]-PhNH	Br	C ₂₇ H ₃₀ BrN ₅ O
271112	4-(8-quinolyl)-PhNH	Cl	C ₂₉ H ₂₈ ClN ₅ O

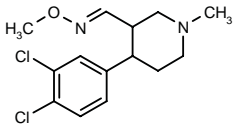
SOURCE – SmithKline Beecham.

REFERENCES

1. Gaster, L.M. et al. (SmithKline Beecham plc) *Indole derivs. having combined 5HT_{1A}, 5HT_{1B} and 5HT_{1D} receptor antagonist activity.* WO 9850358.

271374

4-(3,4-Dichlorophenyl)-1-methyl-3-piperidinecarbaldehyde *O*-methyloxime



C14 H18 Cl2 N2 O; Mol wt: 301.2152

ACTION – Agent for the treatment of CNS disorders including depression, Parkinson’s disease, cognitive disorders and obesity, a specifically claimed compound within a series of piperidine derivatives proven to inhibit the reuptake of the neurotransmitters dopamine, norepinephrine and 5-HT with IC₅₀ values of 0.024, 0.014 and 0.12 nM, respectively.

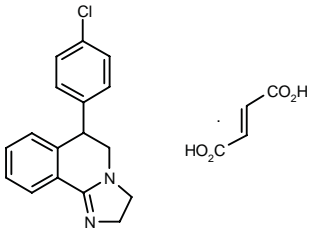
SOURCE – NeuroSearch.

REFERENCES

1. Moldt, P. et al. (NeuroSearch A/S) *Piperidine derivs. as neurotransmitter re-uptake inhibitors.* WO 9851668.

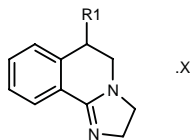
271442

(+)-6-(4-Chlorophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*a*]-isoquinoline fumarate



C17 H15 Cl N2 . C4 H4 O4; Mol wt: 398.8441

ACTION – Antidepressant, a dopamine, norepinephrine and 5-HT reuptake inhibitor (pK_i = 7.2, 8.15 and 7.0, respectively). Other specifically claimed tetrahydroimidazo[2,1-*a*]isoquinoline derivatives include the following:



Compound	R1	X	Isomer	Formula
271443	4-F-Ph	maleate		C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271444	4-Cl-Ph	fumarate	(-)	C ₁₇ H ₁₅ ClN ₂ .C ₄ H ₄ O ₄
271445	4-Me-Ph	maleate		C ₁₈ H ₁₈ N ₂ .C ₄ H ₄ O ₄
271446	4-F-Ph	fumarate	(+)	C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271447	4-F-Ph	fumarate	(-)	C ₁₇ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
271448	2-Naph	fumarate		C ₂₁ H ₁₈ N ₂ .C ₄ H ₄ O ₄

SOURCE – Akzo Nobel.

REFERENCES

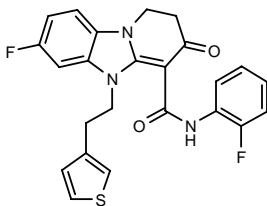
1. Leysen, D. and Ruigt, G.S.F. (Akzo Nobel N.V.) *Tetrahydroimidazo(2,1-a)isoquinoline derivs.* EP 887349.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

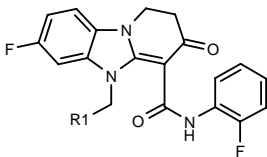
271826

7-Fluoro-*N*-(2-fluorophenyl)-3-oxo-5-[2-(3-thienyl)ethyl]-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole-4-carboxamide



C24 H19 F2 N3 O2 S; Mol wt: 451.4951

ACTION – Agent with high affinity for the benzodiazepine binding site on GABA_A receptors, as demonstrated in a binding assay using [³H]-flunitrazepam as the radioligand (IC₅₀ = 0.096 nM), with potential as a muscle relaxant, sedative, anxiolytic, anticonvulsant and antiepileptic agent and for managing alcoholism and drug overdose. Anticonvulsant activity was demonstrated by inhibition of pentylenetetrazol-induced convulsions in mice (ED₅₀ = 0.1 mg/kg i.p.). Compound also exhibited anxiolytic activity in a rat conflict test. Other specifically claimed compounds within this series of 3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole-4-carboxamide derivatives include the following:



Compound	R1	Formula
271827	2-thienyl-CH2	C ₂₄ H ₁₉ F ₂ N ₃ O ₂ S
271828	2-thienyl	C ₂₃ H ₁₇ F ₂ N ₃ O ₂ S
271829	3-thienyl	C ₂₃ H ₁₇ F ₂ N ₃ O ₂ S
271830	4-imidazolyl	C ₂₂ H ₁₇ F ₂ N ₃ O ₂

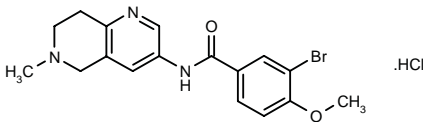
SOURCE – Ortho-McNeil.

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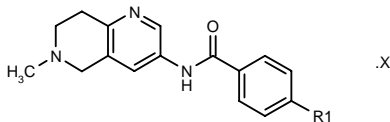
271876

3-Bromo-4-methoxy-N-(6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)benzamide hydrochloride



C17 H18 Br N3 O2 . HCl; Mol wt: 412.7131

ACTION – Anticonvulsant also reported to be useful in the treatment or prevention of anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, Alzheimer’s disease, Parkinson’s disease, sleep disorders and traumatic brain injury. Compound exhibits high affinity for the [³H]-SB-204269 binding site in rat forebrain membranes (pK_i > 8). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) threshold test in mice, where it gave a 177% increase in seizure threshold at 10 mg/kg p.o. Other specifically claimed compounds from this series of substituted 5,6,7,8-tetrahydro[1,6]naphthyridines include the following:



Compound	R1	X	Formula
271877	H		C ₁₆ H ₁₇ N ₃ O
271878	OEt	HCl	C ₁₈ H ₂₁ N ₃ O ₂ .HCl

SOURCE – SmithKline Beecham.

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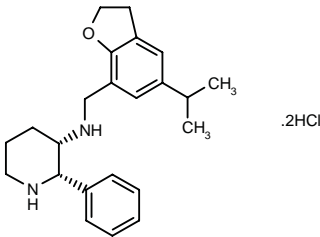
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TREATMENT OF NAUSEA AND VOMITING

HSP-117*

244280

(2*S*,3*S*)-3-(5-Isopropyl-2,3-dihydrobenzofuran-7-ylmethylamino)-2-phenylpiperidine dihydrochloride



C23 H30 N2 O . 2HCl; Mol wt: 423.4248

ACTION – A potent, broad-spectrum antiemetic agent, a nonpeptide tachykinin NK₁ receptor antagonist with affinity for NK₁ receptors in human lymphoblast IM-9 cell membranes about 50-fold higher than the reference compound CP-99994. In functional studies in ferret nucleus tractus solitarius slices, compound antagonized substance P-evoked firing responses at a concentration of 10 μM. When it was administered to ferrets i.c.v. at a dose of 100 μg, it completely inhibited emesis induced by morphine or copper sulfate and was more potent than CP-99994.

SOURCE – Hisamitsu.

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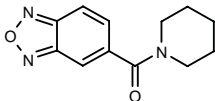
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2. Saito, R. et al. Anti-emetic effects of a novel NK-1 receptor antagonist HSP-117 in ferrets. Neurosci Lett 1998, 254(3): 169.

*Identified compound 244280 (see 242873) Drug Data Report 1997, 019(02): 0128.

COGNITION-ENHANCING DRUGS

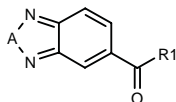
271089

2,1,3-Benzoxadiazol-5-yl(piperidin-1-yl)methanone



C12 H13 N3 O2; Mol wt: 231.2537

ACTION – Agent that enhances synaptic responses mediated by AMPA receptors, potentially useful for the treatment of memory impairment or other cognitive disorders and schizophrenia. *In vitro* activity was demonstrated by a concentration-dependent increase in the amplitude of excitatory postsynaptic potential (EPSP) in rat hippocampus slices, compound being effective at concentrations as low as 3 μ M. *In vivo* efficacy was demonstrated in animal models of schizophrenia, depression and memory enhancement. Other specifically claimed compounds within this series of benzofurazan derivatives include the following:



Compound	A	R1	Formula
271090	S	1-Pip	C ₁₂ H ₁₃ N ₃ OS
271091	O	4-F-1,2,3,6-tetrahydro-1-Pyr	C ₁₂ H ₁₀ FN ₃ O ₂
271092	O	1,2,5,6-tetrahydro-1-Pyr	C ₁₂ H ₁₁ N ₃ O ₂
271093	O	4,4-(F)2-1-Pip	C ₁₂ H ₁₁ F ₂ N ₃ O ₂
271094	O	4-F-1-Pip	C ₁₂ H ₁₂ FN ₃ O ₂
271095	O	4-CN-1-Pip	C ₁₃ H ₁₂ N ₄ O ₂
271189	O	4-OH-1-Pip	C ₁₂ H ₁₃ N ₃ O ₃
271190	O	4-morpholinyl	C ₁₁ H ₁₁ N ₃ O ₃
271191	O	4-thiomorpholinyl	C ₁₁ H ₁₁ N ₃ O ₂ S
271192	O	4-oxo-1-Pip	C ₁₂ H ₁₁ N ₃ O ₃

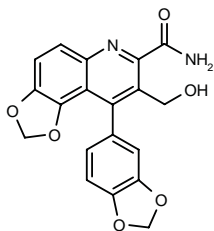
SOURCE – Cortex.

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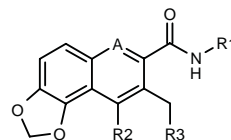
271122

9-(1,3-Benzodioxol-5-yl)-8-(hydroxymethyl)[1,3]-dioxolo[4,5-f]quinoline-7-carboxamide



C₁₉ H₁₄ N₂ O₆; Mol wt: 366.3276

ACTION – Agent able to induce cell differentiation or enhance the cell differentiation-inducing activity of substances such as bone morphogenetic protein (BMP) and neurotrophic factor (NTF). Potentially useful for the treatment of neurodegenerative disorders such as dementia, Alzheimer's disease, amyotrophic lateral sclerosis, diabetic peripheral neuropathy and Parkinson's disease, as well as bone/joint diseases. Within this series of amide derivatives, the following are also included:



Compound	R1	R2	R3	A	Formula
271123	Me	1,3-benzodioxol-5-yl	OH	CH	C ₂₁ H ₁₇ NO ₆
271124	Me	4-Me-O-Ph	OH	CH	C ₂₁ H ₁₉ NO ₅
271125	Me	2-Naph	OH	CH	C ₂₄ H ₁₉ NO ₄
271126	Me	4-F-Ph	OH	CH	C ₂₀ H ₁₆ FNO ₄
271127	Me	4-Me-Ph	OH	CH	C ₂₁ H ₁₉ NO ₄
271128	H	1,3-benzodioxol-5-yl	H	N	C ₁₉ H ₁₄ N ₂ O ₅

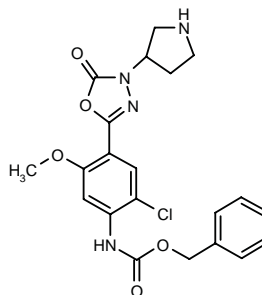
SOURCE – Takeda.

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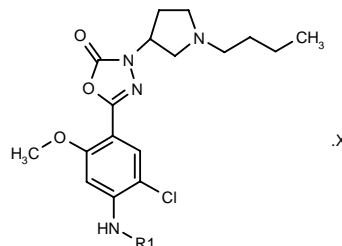
271503

N-[2-Chloro-5-methoxy-4-[5-oxo-4-(3-pyrrolidinyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]phenyl]carbamic acid benzyl ester

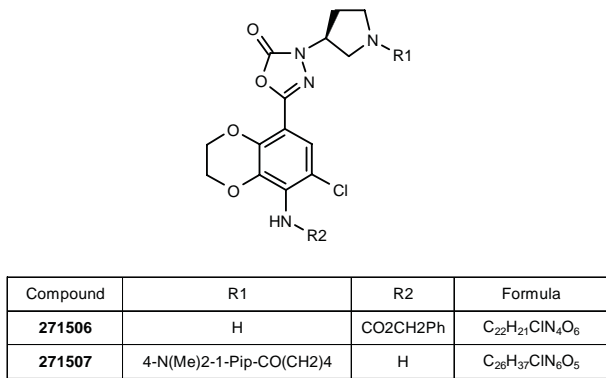


C₂₁ H₂₁ Cl N₄ O₅; Mol wt: 444.8729

ACTION – 5-HT₄ receptor ligand with an IC₅₀ value of 0.7–15 nM in a binding assay using guinea pig striatum preparations and [³H]-GR-113808 as the ligand. Potentially useful in the treatment of CNS disorders such as cognitive disorders, psychoses, obsessive-compulsive disorder, depression and anxiety, gastrointestinal, cardiovascular and urinary disorders. Within this series of 3-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one derivatives, the following are also included:



Compound	R1	X	Formula
271504	CO ₂ CH ₂ Ph		C ₂₅ H ₂₉ ClN ₄ O ₅
271505	H	HBr	C ₁₇ H ₂₃ ClN ₄ O ₃ ·HBr



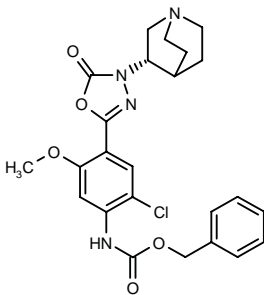
SOURCE – Synthélabo.

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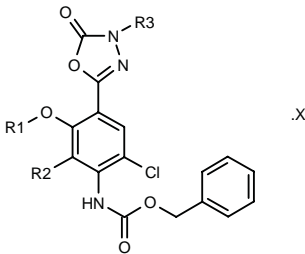
271537

N-[2-Chloro-5-methoxy-4-[5-oxo-4-[3(S)-quinuclidinyl]-4,5-dihydro-1,3,4-oxadiazol-2-yl]phenyl]carbamic acid benzyl ester

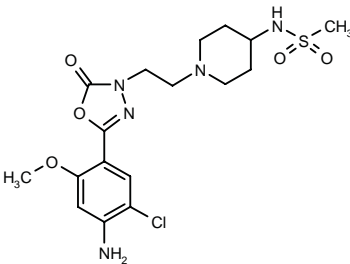


C24 H25 Cl N4 O5; Mol wt: 484.9375

ACTION – Agent for the treatment of disorders of the CNS, gastrointestinal, cardiovascular or urinary systems including cognitive disorders, obsessive–compulsive disorder, schizophrenia, anxiety, depression, irritable bowel syndrome, diarrhea, cardiac arrhythmias and urinary incontinence, with affinity for 5-HT₄ receptors. Within this series of 5-phenyl-1,3,4-oxadiazol-2(3H)-one derivatives, the following are also included:



Compound	R1	R2	R4	X	Formula
271538	-CH2CH2O-		(R)-1-azabicyclo-[2.2.2]oct-3-yl		C ₂₅ H ₂₅ ClN ₄ O ₆
271539	Me	H	1-Pip-CH2CH2	HCl	C ₂₄ H ₂₇ ClN ₄ O ₅ .HCl
271540	-CH2CH2O-		4-(5H-4-imidazolyl)-1-Pip-CH2CH2		C ₂₈ H ₂₉ ClN ₆ O ₆
271542	Me	H	4-(AcNH)-1-Pip-CH2CH2		C ₂₆ H ₃₀ ClN ₅ O ₆



271544: C17 H24 Cl N5 O5 S

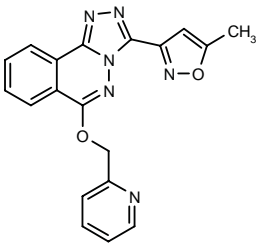
SOURCE – Synthélabo.

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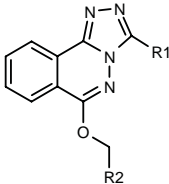
271582

3-(5-Methyl-3-isoxazolyl)-6-(2-pyridinylmethoxy)[1,2,4]-triazolo[3,4-a]phthalazine



C19 H14 N6 O2; Mol wt: 358.3596

ACTION – Cognition-enhancing agent with affinity for GABA_A receptors containing the α5 subunit (K_i = 100 nM or less) and reported to possess lower affinity for α1, α2 and/or α3 binding sites, thus expected to be associated with little or no proconvulsant effect. Within this series of substituted 1,2,4-triazolo[3,4-a]phthalazine derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
271583	5-Me-3-isoxazolyl	1-Me-1,2,4-triazol-3-yl	C ₁₇ H ₁₄ N ₈ O ₂
271584	3-Me-5-isoxazolyl	1-Me-1,2,4-triazol-3-yl	C ₁₇ H ₁₄ N ₈ O ₂
271585	5-Me-3-isoxazolyl	1-Me-4-imidazolyl	C ₁₈ H ₁₅ N ₇ O ₂
271586	5-Me-3-isoxazolyl	1-Me-1,2,3-triazol-4-yl	C ₁₇ H ₁₄ N ₈ O ₂

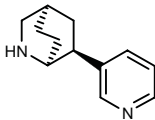
SOURCE – Merck Sharp & Dohme.

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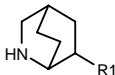
271590

endo-6-(3-Pyridyl)-2-azabicyclo[2.2.2]octane

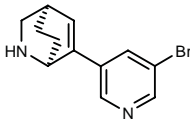


C12 H16 N2; Mol wt: 188.2724

ACTION – Nicotinic acetylcholine receptor agonist, as demonstrated in a binding assay by 94% inhibition of [³H]-cytidine binding to nicotinic acetylcholine receptors in rat whole brain homogenates at a concentration of 10 nM. Potentially useful in the treatment of neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease, and as an analgesic agent. Other compounds from this series of 2-azabicyclo derivatives include the following:



Compound	R1	Isomer	Formula
271591	5-pyrimidinyl	endo	C ₁₁ H ₁₅ N ₃
271593	5-ethynyl-3-Pyr		C ₁₄ H ₁₆ N ₂



271592: C12 H13 Br N2

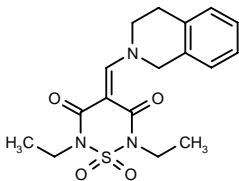
SOURCE – Sumitomo Pharmaceuticals.

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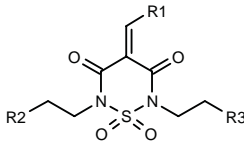
271620

2,6-Diethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-ylmethylene)perhydro-1,2,6-thiadiazine-3,5-dione *S,S*-dioxide



C17 H21 N3 O4 S; Mol wt: 363.4359

ACTION – Agent for the treatment of neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease, as well as depression and obesity, that acts as a ligand inhibitor of the corticotropin-releasing factor (CRF)/CRF-binding protein complex, thus increasing the levels of free CRF. A representative compound from a series of thiadiazinyl derivatives, wherein the following are also included:



Compound	R1	R2=R3	Formula
271621	2-benzimidazolyl-NH	Ph	C ₂₇ H ₂₅ N ₅ O ₄ S
271622	2-benzimidazolyl-NH	H	C ₁₅ H ₁₇ N ₅ O ₄ S
271623	4-(2-Pyr)-1-Piz	H	C ₁₇ H ₂₃ N ₅ O ₄ S
271624	cyclopropyl-NH	H	C ₁₁ H ₁₇ N ₃ O ₄ S
271625	4-morpholinyl	H	C ₁₂ H ₁₃ N ₃ O ₅ S
271626	3H-5-tetrazolyl-NH	H	C ₉ H ₁₃ N ₇ O ₄ S
271630	4-(2-OH-Ph)-1-Piz	2-thienyl	C ₂₆ H ₂₆ N ₄ O ₅ S ₃
271631	ethynyl-CH2NH	2-thienyl	C ₁₉ H ₁₉ N ₃ O ₄ S ₃
271632	2-furyl-CH2NH	Ph	C ₂₅ H ₂₅ N ₃ O ₅ S
271633	cyclohexyl-S	Ph	C ₂₆ H ₃₀ N ₂ O ₄ S ₂
271634	SC6H13	Ph	C ₂₆ H ₃₂ N ₂ O ₄ S ₂

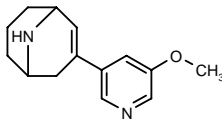
SOURCE – Lilly.

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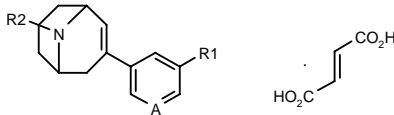
271871

(±)-3-(5-Methoxy-3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ene



C14 H18 N2 O; Mol wt: 230.3092

ACTION – Agent with high affinity for neuronal nicotinic acetylcholine receptors (nAChRs), as demonstrated in binding assays by IC₅₀ values of 0.0030 μM against [³H]-cytisine binding in rat cortical preparations, 0.0180 μM against [³H]-epibatidine binding in rat forebrain preparations and 0.0170 μM against [³H]-α-bungarotoxin binding in rat cortical preparations. Potentially useful in the treatment of CNS disorders such as Alzheimer’s disease, Parkinson’s disease, memory disturbances and attention deficit hyperactivity disorder, pain and inflammation, and as an aid in smoking cessation. Other compounds within this series of 9-azabicyclo[3.3.1]non-2-ene and nonane derivatives include the following:



Compound	R1	R2	A	Formula
271872	OMe	Me	N	C ₁₅ H ₂₀ N ₂ O ₂ C ₄ H ₄ O ₄
271873	NH2	Me	CH	C ₁₅ H ₂₀ N ₂ ·C ₄ H ₄ O ₄
271874	H	H	N	C ₁₃ H ₁₆ N ₂ ·C ₄ H ₄ O ₄
271875	H	Me	N	C ₁₄ H ₁₈ N ₂ ·C ₄ H ₄ O ₄

SOURCE – NeuroSearch.

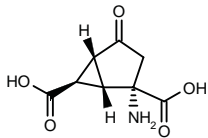
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TREATMENT OF
CEREBROVASCULAR DISEASES

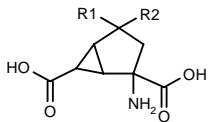
270548

(1*S**,2*S**,5*R**,6*R**)-2-Amino-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C8 H9 N O5; Mol wt: 199.1611

ACTION – Agent for the treatment of neurological disorders characterized by excessive or inappropriate stimulation of excitatory amino acid transmission such as acute and chronic neurodegenerative conditions, as well as psychosis, convulsions, pain, anxiety, depression and emesis, that acts as a modulator of metabotropic glutamate receptors. Other specifically claimed compounds include the following:



Compound	R1	R2	Isomer	Formula
270549	-(E)-N(OH)-		1 <i>S</i> *,2 <i>S</i> *,5 <i>R</i> *,6 <i>R</i> *	C ₈ H ₁₀ N ₂ O ₅
270550	-(Z)-N(OH)-		1 <i>S</i> *,2 <i>S</i> *,5 <i>R</i> *,6 <i>R</i> *	C ₈ H ₁₀ N ₂ O ₅
270551	F	H	1 <i>S</i> *,2 <i>R</i> *,4 <i>S</i> *,5 <i>S</i> *,6 <i>S</i> *	C ₈ H ₁₀ FNO ₄
270552	-CH(CO ₂ H)-		1 <i>S</i> *,2 <i>S</i> *,5 <i>R</i> *,6 <i>S</i> *	C ₁₀ H ₁₁ NO ₆
270553	-CH ₂ -		1 <i>S</i> *,2 <i>S</i> *,5 <i>R</i> *,6 <i>S</i> *	C ₉ H ₁₁ NO ₄

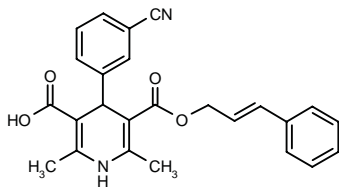
SOURCE – Lilly.

REFERENCES

1. Massey, S.M. et al. (Eli Lilly and Company) *Excitatory amino acid receptor modulators.* EP 878463.

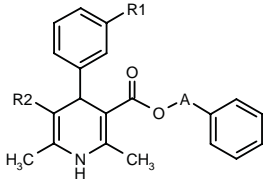
271029

4-(3-Cyanophenyl)-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylic acid mono[3-phenyl-2(*E*)-propenyl]-ester



C25 H22 N2 O4; Mol wt: 414.4588

ACTION – N- and L-type calcium channel inhibitor with potential in the treatment of disorders such as stroke and Alzheimer's disease. A representative compound from a series of 1,4-dihydropyridine derivatives, wherein the following are also included:



Compound	R1	R2	A	Formula
271030	Cl	CONH ₂	-CH ₂ CH=CH-	C ₂₄ H ₂₃ ClN ₂ O ₃
271031	Cl	CN	-CH ₂ CH=CH-	C ₂₄ H ₂₁ ClN ₂ O ₂
271032	Cl	CO ₂ H	-CH ₂ CONH-	C ₂₃ H ₂₁ ClN ₂ O ₅
271033	OMe	CO ₂ H	-CH ₂ CH=CH-	C ₂₈ H ₂₈ NO ₅

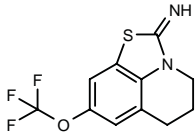
SOURCE – Ajinomoto.

REFERENCES

1. Uneyama, H. et al. (Ajinomoto Co., Inc.) *Novel dihydropyridine deriv.* WO 9849144.

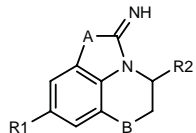
271066

8-(Trifluoromethoxy)-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]-quinolin-2-imine

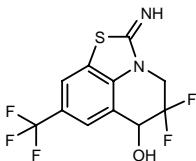


C11 H9 F3 N2 O S; Mol wt: 274.2651

ACTION – Glutamate antagonist potentially useful as an anticonvulsant and antiischemic agent, as well as for the treatment of neurodegenerative disorders, pain, migraine, anxiety, depression, sleep disorders and drug or alcohol withdrawal symptoms. Other specifically claimed compounds from this series of thiazolobenzoheterocycles include the following:



Compound	R1	R2	A	B	Formula
271067	CF ₃	H	-S-	-CH ₂ -	C ₁₁ H ₇ F ₃ N ₂ S
271068	CF ₃	Me	-S-	-CH ₂ -	C ₁₂ H ₁₁ F ₃ N ₂ S
271069	OCF ₃	H	-S-	-CO-	C ₁₁ H ₇ F ₃ N ₂ O ₂ S
271070	OCF ₃	H	-S-	SO ₂	C ₁₀ H ₇ F ₃ N ₂ O ₃ S ₂
271071	OCF ₃	H	-S-	-SO-	C ₁₀ H ₇ F ₃ N ₂ O ₂ S ₂
271072	CF ₃	H	-S-	-SO-	C ₁₀ H ₇ F ₃ N ₂ OS ₂
271073	CF ₃	H	-S-	-S-	C ₁₀ H ₇ F ₃ N ₂ S ₂
271074	CF ₃	H	-S-	-CH(Ph)-	C ₁₇ H ₁₃ F ₃ N ₂ S
271075	OCF ₃	H	-S-	-O-	C ₁₀ H ₇ F ₃ N ₂ O ₂ S
271076	CF ₃	CH ₂ OH	-S-	-CH ₂ -	C ₁₂ H ₁₁ F ₃ N ₂ OS
271077	CF ₃	H	-S-	-CH(OH)-	C ₁₁ H ₇ F ₃ N ₂ OS
271078	CF ₃	CH ₂ N(Me)Et	-S-	-CH ₂ -	C ₁₅ H ₁₈ F ₃ N ₃ S
271079	CF ₃	H	-Se-	-CH ₂ -	C ₁₁ H ₉ F ₃ N ₂ Se
271080	CF ₃	H	-S-	-CH(SOEt)-	C ₁₃ H ₁₃ F ₃ N ₂ OS ₂
271081	CF ₃	H	-S-	-CH(SO ₂ Et)-	C ₁₃ H ₁₃ F ₃ N ₂ O ₂ S ₂



271077: C11 H7 F5 N2 O S

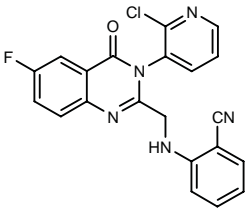
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Hardy, J.-C. et al. (Rhône-Poulenc Rorer SA) *Thiazolobenzoheterocycles, preparation and medicines containing same*. WO 9838194.

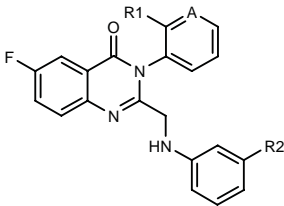
271273

2-[3-(2-Chloropyridin-3-yl)-6-fluoro-4-oxo-3,4-dihydro-quinazolin-2-ylmethylamino]benzonitrile

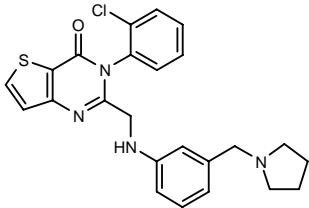


C21 H13 Cl F N5 O; Mol wt: 405.8187

ACTION – Neuroprotective agent, a potent AMPA receptor antagonist with an IC₅₀ value < 5 µM against AMPA receptor activation-induced ⁴⁵Ca²⁺ uptake in rat cerebellar granule cell cultures. Other specifically claimed compounds from this series of quinazolin-4(3*H*)-one derivatives include the following:



Compound	R1	R2	A	Formula
271274	Cl	CN	CH	C ₂₂ H ₁₄ ClFN ₄ O
271275	Cl	CH ₂ N(Et) ₂	CH	C ₂₆ H ₂₆ ClFN ₄ O
271276	Me	1-pyrrolidinyl-CH ₂	N	C ₂₆ H ₂₆ FN ₅ O
271277	Cl	NHAc	CH	C ₂₃ H ₁₈ ClFN ₄ O ₂
271278	Cl	1-pyrrolidinyl-CH ₂	CH	C ₂₆ H ₂₄ ClFN ₄ O



271279: C24 H23 Cl N4 O S

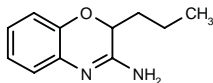
SOURCE – Pfizer.

REFERENCES

1. Chenard, B.L. et al. (Pfizer Products Inc.) *Quinazolin-4-one AMPA antagonists*. EP 884310, JP 99012255.

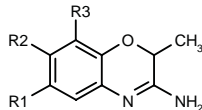
271298

2-Propyl-2*H*-1,4-benzoxazin-3-amine



C11 H14 N2 O; Mol wt: 190.2446

ACTION – Agent for the treatment of neurodegenerative, inflammatory, autoimmune and cardiovascular disorders, a selective inhibitor of neuronal nitric oxide synthase (nNOS; IC₅₀ = 1.2 µM vs. > 10 µM for endothelial enzyme [eNOS] and > 100 µM for inducible enzyme [iNOS]). Other compounds within this series of substituted heterocycles include the following:



Compound	R1=R2	R3	Formula
271299	Me	H	C ₁₁ H ₁₄ N ₂ O
271300	H	Me	C ₁₀ H ₁₂ N ₂ O

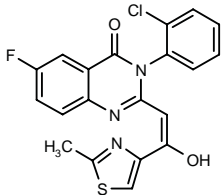
SOURCE – Schering AG.

REFERENCES

1. Hölscher, P. et al. (Schering AG) *Substd. heterocycles and their use in medicaments*. WO 9850372.

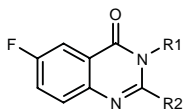
271311

3-(2-Chlorophenyl)-6-fluoro-2-[2-hydroxy-2-(2-methyl-thiazol-4-yl)vinyl]quinazolin-4(3*H*)-one



C20 H13 Cl F N3 O2 S; Mol wt: 413.8587

ACTION – Neuroprotective agent, a potent AMPA receptor antagonist. Other specifically claimed compounds from this series of quinazolin-4(3*H*)-one derivatives include the following:



Compound	R1	R2	Formula
271312	2-Cl-Ph	6-Me-2-Pyr-C(OH)=CH	C ₂₂ H ₁₅ ClFN ₃ O ₂
271313	2-Cl-Ph	3-CN-6-Me-2-Pyr-C(OH)=CH	C ₂₃ H ₁₄ ClFN ₄ O ₂
271314	2-Cl-Ph	3-CN-2-Pyr-C(OH)=CH	C ₂₂ H ₁₂ ClFN ₄ O ₂
271315	2-Cl-Ph	2-CN-PhC(OH)=CH	C ₂₃ H ₁₃ ClFN ₃ O ₂
271316	2-Cl-3-Pyr	3-CN-2-Pyr-C(OH)=CH	C ₂₁ H ₁₁ ClFN ₅ O ₂
271317	2-Cl-3-Pyr	3-CN-6-Me-2-Pyr-C(OH)=CH	C ₂₂ H ₁₃ ClFN ₅ O ₂
271318	2-Cl-Ph	2-Pyr-C(OH)=CH	C ₂₁ H ₁₃ ClFN ₃ O ₂
271319	2-Me-3-Pyr	2-CN-PhC(OH)=CH	C ₂₃ H ₁₅ FN ₄ O ₂
271320	2-Cl-3-Pyr	2-CN-PhC(OH)=CH	C ₂₂ H ₁₂ ClFN ₄ O ₂
271321	2-Cl-Ph	2-F-PhCH(OH)CH ₂	C ₂₂ H ₁₅ ClF ₂ N ₂ O ₂

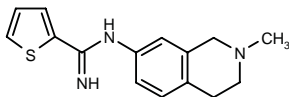
SOURCE – Pfizer.

REFERENCES

1. Chenard, B.L. and Welch, W.M. Jr. (Pfizer Products Inc.) *Quinazoline-4-one AMPA antagonists*. EP 884316.

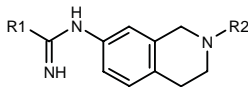
271497

N-(2-Methyl-1,2,3,4-tetrahydro-7-isoquinoliny)thiophene-2-carboxamide



C15 H17 N3 S; Mol wt: 271.3863

ACTION – Inhibitor of the neuronal isoform of nitric oxide synthase (nNOS) with an IC₅₀ value < 10 μM, particularly useful for the treatment or prophylaxis of hypoxia, stroke, ischemia, neurodegenerative conditions, schizophrenia and pain. Other specifically claimed amidine derivatives include the following:



Compound	R1	R2	Formula
271498	2-thienyl	i-Pr	C ₁₇ H ₂₁ N ₃ S
271499	2-thienyl	Et	C ₁₆ H ₁₉ N ₃ S
271500	2-thienyl	Pr	C ₁₇ H ₂₁ N ₃ S
271501	3-thienyl	Me	C ₁₅ H ₁₇ N ₃ S
271502	2-thienyl	Bu	C ₁₈ H ₂₃ N ₃ S

SOURCE – Astra.

REFERENCES

1. MacDonald, J. et al. (Astra AB) *Compounds*. WO 9850380.

271561

CysteinyI-isoleucyl-alanyl-lysyl-aspartyl-tyrosyl-glycyl-arginyI-cysteinyI-lysyl-tryptophanyl-glycyl-glycyl-tyrosyl-prolyl-cysteinyI-cysteinyI-arginyI-glycyl-arginyI-glycyl-cysteinyI-isoleucyl-cysteinyI-seryl-isoleucyl-methionyl-glycyl-threonyI-asparaginyI-cysteinyI-glutamyl-cysteinyI-lysinaMide cyclic (S-3.1-S-3.17:S-3.9-S-3.22:S-3.16-S-3.33:S-3.24-S-3.31)-disulfide

C152 H237 N49 O43 S9 ; Mol wt: 3727.4383

ACTION – Neuroprotective and analgesic peptide that acts by blocking neuronal calcium channels, as demonstrated *in vitro* in nerve cells isolated from rat spinal cord dorsal root ganglionic neurons at a concentration of 1 μM. Another related peptide is:

CysteinyI-isoleucyl-alanyl-lysyl-aspartyl-tyrosyl-glycyl-arginyI-cysteinyI-lysyl-tryptophanyl-glycyl-glycyl-threonyI-prolyl-cysteinyI-cysteinyI-arginyI-glycyl-arginyI-glycyl-cysteinyI-isoleucyl-cysteinyI-seryl-isoleucyl-methionyl-glycyl-threonyI-asparaginyI-cysteinyI-glutamyl-cysteinyI-lysinaMide cyclic (S-3.1-S-3.17:S-3.9-S3.22:S-3.16-S-3.33:S-3.24-S-3.31)-disulfide

271562: C147 H235 N49 O43 S9

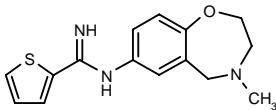
SOURCE – Mitsubishi Chemical.

REFERENCES

1. Konishi, S. et al. (Mitsubishi Chemical Corp.) *Novel peptides*. JP 98287698.

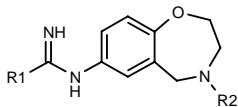
271563

N-(4-Methyl-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-thiophene-2-carboxamide



C15 H17 N3 O S; Mol wt: 287.3853

ACTION – A selective inhibitor of the neuronal isoform of nitric oxide synthase (nNOS) with potential in the treatment or prevention of hypoxia, stroke, ischemia, neurodegenerative disorders such as amyotrophic lateral sclerosis, Huntington’s disease or Parkinson’s disease, as well as schizophrenia and pain. Other specifically claimed compounds within this series of amidine derivatives include the following:



Compound	R1	R2	Formula
271546	2-thienyl	Et	C ₁₆ H ₁₉ N ₃ OS
271547	2-thienyl	Pr	C ₁₇ H ₂₁ N ₃ OS
271548	2-thienyl	i-Pr	C ₁₇ H ₂₁ N ₃ OS
271550	2-thienyl	H	C ₁₄ H ₁₅ N ₃ OS
271551	3-thienyl	H	C ₁₄ H ₁₅ N ₃ OS
271552	3-thienyl	Me	C ₁₅ H ₁₇ N ₃ OS

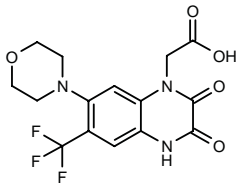
SOURCE – Astra.

REFERENCES

1. MacDonald, J. et al. (Astra AB) *Amidide derivs. as inhibitors of nitric oxide synthase*. WO 9850382.

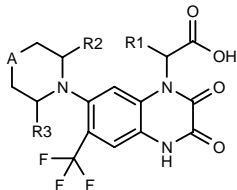
271822

2-[7-(4-Morpholinyl)-2,3-dioxo-6-(trifluoromethyl)-1,2,3,4-dihydro-1-quinoxaliny]acetic acid



C15 H14 F3 N3 O5; Mol wt: 373.2856

ACTION – Selective AMPA receptor antagonist reported to possess very good water solubility, potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, anoxia, hypoxia, epilepsy, anxiety, schizophrenia, migraine and pain. Other specifically claimed compounds within this series of quinoxalinedione derivatives include the following:



Compound	R1	R2	R3	A	Formula
271823	H	H	H	S	C ₁₅ H ₁₄ F ₃ N ₃ O ₄ S
271824	H	Me	Me	O	C ₁₇ H ₁₈ F ₃ N ₃ O ₅
271825	Me	H	H	O	C ₁₆ H ₁₆ F ₃ N ₃ O ₅

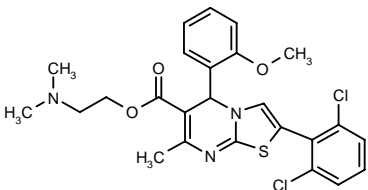
SOURCE – Schering AG.

REFERENCES

1. Huth, A. et al. (Schering AG) *New quinoxaline dione derivs., the production thereof and use of the same in medicaments*. WO 9900384.

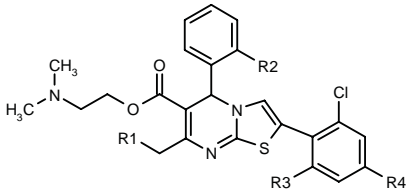
271852

2-(2,6-Dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid 2-(dimethyl-amino)ethyl ester



C25 H25 Cl2 N3 O3 S; Mol wt: 518.4625

ACTION – Group II metabotropic glutamate receptor (mGluR₂ and mGluR₃) antagonist, claimed for the treatment or prevention of acute or chronic neurological disorders, muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, anxiety, psychoses, depression, pain and vomiting. Within this series of 5H-thiazolo[3,2-a]pyrimidine derivatives, the following compounds are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
271853	H	OMe	H	Cl	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₃ S
271854	H	Cl	Cl	H	C ₂₄ H ₂₂ Cl ₃ N ₃ O ₂ S
271855	Me	OMe	Cl	H	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₃ S
271856	H	i-PrO	Cl	H	C ₂₇ H ₂₉ Cl ₂ N ₃ O ₃ S
271857	Me	OMe	H	Cl	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₃ S

SOURCE – Roche.

REFERENCES

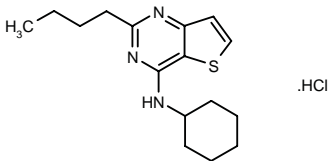
1. Adam, G. et al. (F. Hoffmann-La Roche AG) *5H-Thiazolo(3,2-a)pyrimidine derivs*. EP 891978.

RESPIRATORY DRUGS

ASTHMA THERAPY

269357

N-(2-Butylthieno[3,2-d]pyrimidin-4-yl)-N-cyclohexylamine hydrochloride



C16 H23 N3 S . HCl; Mol wt: 325.9056

ACTION – Potent inhibitor of phosphodiesterase type 4 (PDE4) with potency (IC₅₀ = 0.4 ± 0.2 μM against guinea pig ventricular PDE4) and PDE3 selectivity (IC₅₀ > 200 μM) comparable to the standard PDE4 inhibitor rolipram. Compound exhibited affinity for the [³H]-rolipram binding site about 30-40-fold less than that of rolipram and RS-14491, indicating a reduced liability for inducing emesis. It potentiated isoprenaline-induced cAMP accumulation in guinea pig eosinophils (IC₅₀ = 0.56 μM), indicating efficient cell penetration and promising therapeutic activity in allergic asthma. Other compounds from this series of thieno[3,2-d]pyrimidines selected for *in vivo* evaluation as potential antiasthmatic agents are:

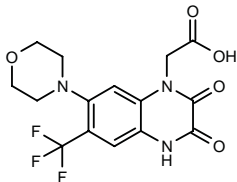
SOURCE – Astra.

REFERENCES

1. MacDonald, J. et al. (Astra AB) *Amidide derivs. as inhibitors of nitric oxide synthase*. WO 9850382.

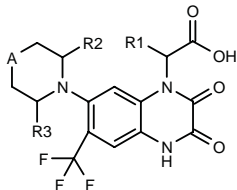
271822

2-[7-(4-Morpholinyl)-2,3-dioxo-6-(trifluoromethyl)-1,2,3,4-dihydro-1-quinoxaliny]acetic acid



C15 H14 F3 N3 O5; Mol wt: 373.2856

ACTION – Selective AMPA receptor antagonist reported to possess very good water solubility, potentially useful in the treatment of neurodegenerative disorders, cerebral ischemia, anoxia, hypoxia, epilepsy, anxiety, schizophrenia, migraine and pain. Other specifically claimed compounds within this series of quinoxalinedione derivatives include the following:



Compound	R1	R2	R3	A	Formula
271823	H	H	H	S	C ₁₅ H ₁₄ F ₃ N ₃ O ₄ S
271824	H	Me	Me	O	C ₁₇ H ₁₈ F ₃ N ₃ O ₅
271825	Me	H	H	O	C ₁₆ H ₁₆ F ₃ N ₃ O ₅

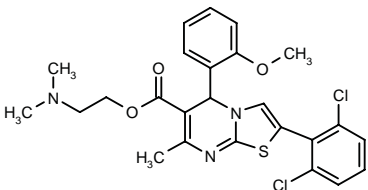
SOURCE – Schering AG.

REFERENCES

1. Huth, A. et al. (Schering AG) *New quinoxaline dione derivs., the production thereof and use of the same in medicaments*. WO 9900384.

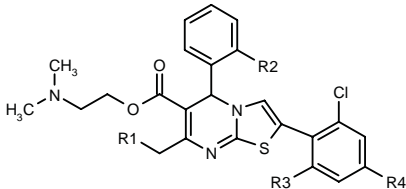
271852

2-(2,6-Dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid 2-(dimethyl-amino)ethyl ester



C25 H25 Cl2 N3 O3 S; Mol wt: 518.4625

ACTION – Group II metabotropic glutamate receptor (mGluR₂ and mGluR₃) antagonist, claimed for the treatment or prevention of acute or chronic neurological disorders, muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, anxiety, psychoses, depression, pain and vomiting. Within this series of 5H-thiazolo[3,2-a]pyrimidine derivatives, the following compounds are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
271853	H	OMe	H	Cl	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₃ S
271854	H	Cl	Cl	H	C ₂₄ H ₂₂ Cl ₃ N ₃ O ₂ S
271855	Me	OMe	Cl	H	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₃ S
271856	H	i-PrO	Cl	H	C ₂₇ H ₂₉ Cl ₂ N ₃ O ₃ S
271857	Me	OMe	H	Cl	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₃ S

SOURCE – Roche.

REFERENCES

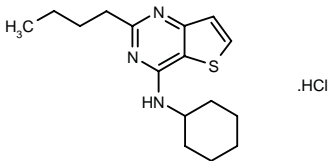
1. Adam, G. et al. (F. Hoffmann-La Roche AG) *5H-Thiazolo(3,2-a)pyrimidine derivs*. EP 891978.

RESPIRATORY DRUGS

ASTHMA THERAPY

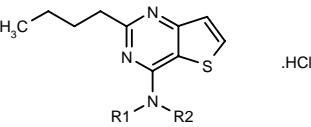
269357

N-(2-Butylthieno[3,2-d]pyrimidin-4-yl)-N-cyclohexylamine hydrochloride



C16 H23 N3 S . HCl; Mol wt: 325.9056

ACTION – Potent inhibitor of phosphodiesterase type 4 (PDE4) with potency (IC₅₀ = 0.4 ± 0.2 μM against guinea pig ventricular PDE4) and PDE3 selectivity (IC₅₀ > 200 μM) comparable to the standard PDE4 inhibitor rolipram. Compound exhibited affinity for the [³H]-rolipram binding site about 30-40-fold less than that of rolipram and RS-14491, indicating a reduced liability for inducing emesis. It potentiated isoprenaline-induced cAMP accumulation in guinea pig eosinophils (IC₅₀ = 0.56 μM), indicating efficient cell penetration and promising therapeutic activity in allergic asthma. Other compounds from this series of thieno[3,2-d]pyrimidines selected for *in vivo* evaluation as potential antiasthmatic agents are:



Compound	R1	R2	Formula
269358	H	Ph	C ₁₆ H ₁₇ N ₃ S.HCl
269359	Me	CH ₂ Ph	C ₁₈ H ₂₁ N ₃ S.HCl

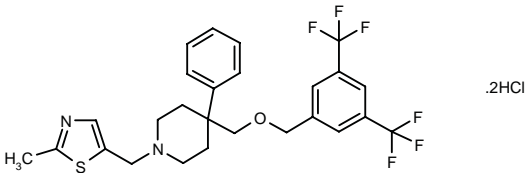
SOURCE – Almirall Prodesfarma.

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270367

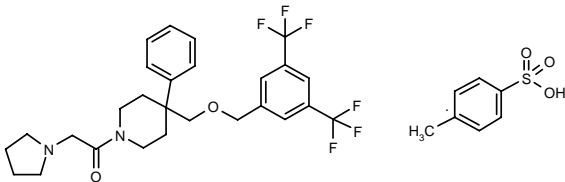
4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-1-(2-methyl-5-thiazolylmethyl)-4-phenylpiperidine dihydrochloride



C26 H26 F6 N2 O S . 2HCl; Mol wt: 601.4802

White needles, m.p. 110-3 °C.

ACTION – Potent, nonpeptide tachykinin NK₁ receptor antagonist with an IC₅₀ value of 2.8 nM against [¹²⁵I]-substance P binding to human receptors expressed in CHO cells. In rats, compound showed good bioavailability and a favorable pharmacokinetic profile. Using the guinea pig resiniferatoxin-induced esophageal plasma extravasation model of NK₁ receptor-antagonist activity, the compound demonstrated potent inhibition, with an ID₅₀ of 0.28 mg/kg p.o., a rapid onset of action and long-lasting activity (significant inhibition at 16 h). Another related compound with a similar profile is:



270368: C27 H30 F6 N2 O2 . C7 H8 O3 S

SOURCE – Merck & Co.

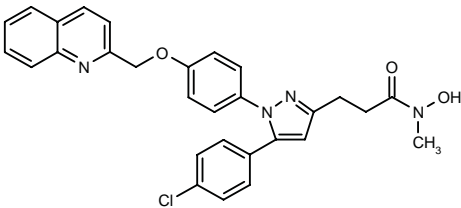
REFERENCES

1. Harrison, T. et al. (Merck Sharp & Dohme Ltd.) *4-Arylmethoxyethyl piperidines as tachykinin antagonists.* EP 666856, JP 96502510, US 5620989, WO 9410165.

2. Stevenson, G.I. et al. *4,4-Disubstituted piperidine high-affinity NK1 antagonists: Structure-activity relationships and in vivo activity.* J Med Chem 1998, 41(23): 4623.

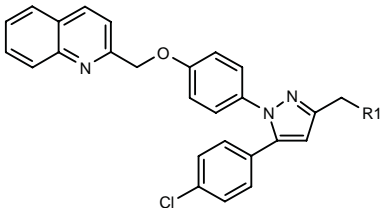
270539

3-[5-(4-Chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]-1H-pyrazol-3-yl]-N-methylpropionohydroxamic acid



C29 H25 Cl N4 O3; Mol wt: 512.9945

ACTION – Antiallergic and antiinflammatory agent, an inhibitor of leukotriene biosynthesis that acts by inhibiting 5-lipoxygenase activity, as demonstrated *in vitro* using enzyme extracted from RBL-1 cells (IC₅₀ = 0.21 μM) or in intact RBL-1 cells (IC₅₀ = 0.49 μM). Other specifically claimed arylpyrazole derivatives include the following:



Compound	R1	Formula
270540	CO ₂ Et	C ₂₉ H ₂₄ ClN ₃ O ₃
270541	CO ₂ H	C ₂₇ H ₂₀ ClN ₃ O ₃
270542	CH ₂ CH=NOH	C ₂₈ H ₂₃ ClN ₄ O ₂
270543	CH ₂ OH	C ₂₇ H ₂₂ ClN ₃ O ₂

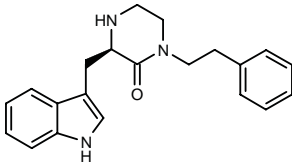
SOURCE – Ortho-McNeil.

REFERENCES

1. Ferro, M.P. and Wachter, M.P. (Ortho Pharmaceutical Corp.) *Arylpyrazoles as leukotriene inhibitors.* US 5843958.

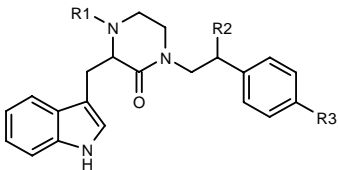
270569

3(R)-(1H-Indol-3-ylmethyl)-1-(2-phenylethyl)-2-piperazinone



C21 H23 N3 O; Mol wt: 333.4327

ACTION – Agent for the treatment of asthma, cough and bronchitis, a tachykinin receptor antagonist. Other specifically claimed heterocyclic substituted piperazinone derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
270570	H	H	H	S	C ₂₁ H ₂₃ N ₃ O
270571	H	H	OCH ₂ Ph	R	C ₂₈ H ₂₉ N ₃ O ₂
270572	H	H	OCH ₂ Ph	S	C ₂₈ H ₂₉ N ₃ O ₂
270573	H	Ph	H	R	C ₂₇ H ₂₇ N ₃ O
270574	H	H	OH	R	C ₂₁ H ₂₃ N ₃ O ₂
270575	H	H	OH	S	C ₂₁ H ₂₃ N ₃ O ₂
270576	3-indolyl-COCH ₂	H	H	R	C ₃₁ H ₃₀ N ₄ O ₂
270577	3-indolyl-COCH ₂	Ph	H	R	C ₃₇ H ₃₄ N ₄ O ₂
270578	3-indolyl-COCH ₂	H	OCH ₂ Ph	R	C ₃₈ H ₃₆ N ₄ O ₃
270579	H-L-PyroGlu-	H	H	R	C ₂₆ H ₂₈ N ₄ O ₃

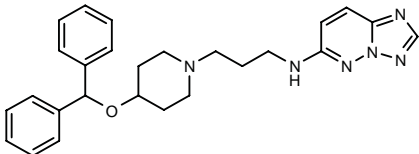
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Burkholder, T.P. et al. (Hoechst Marion Roussel, Inc.) *Heterocyclic subst. piperazinone derivs.* US 5840726.

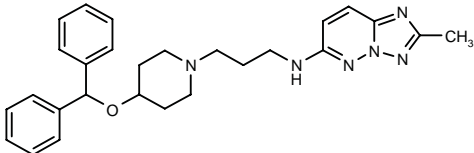
271056

N-[3-[4-(Diphenylmethoxy)-1-piperidiny]propyl]-N-([1,2,4]triazolo[1,5-b]pyridazin-6-yl)amine



C26 H30 N6 O; Mol wt: 442.5640

ACTION – Antiasthmatic and antiallergic agent with antihistaminic and eosinophil chemotaxis-inhibitory activity, as demonstrated by 91% inhibition of histamine-induced skin reactions in guinea pigs at 3 mg/kg p.o. and 64% inhibition of LTB₄-induced guinea pig eosinophil chemotaxis at 10 μM. Within this series of condensed pyridazine derivatives, the following is also included:



271057: C27 H32 N6 O

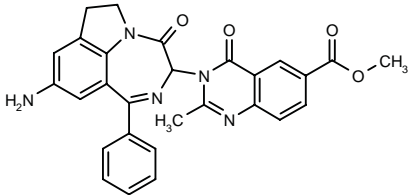
SOURCE – Takeda.

REFERENCES

1. Kawano, Y. et al. (Takeda Chemical Industries, Ltd.) *Condensed pyridazine derivs., their production and use.* WO 9849167.

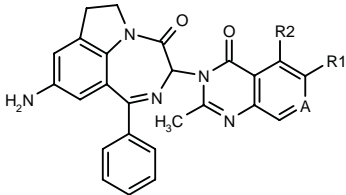
271129

3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid methyl ester enantiomer A



C28 H23 N5 O4; Mol wt: 493.5207

ACTION – Antiinflammatory, antiallergic and antiarthritic agent, a potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.003 μM), with much lower activity against PDE3, PDE1 and PDE5; it inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF-α) production in human whole blood at a concentration of < 5 μM. It is also reported to significantly reduce antigen-induced eosinophil infiltration into bronchoalveolar lavage fluid in an *in vivo* model at a dose of 10 mg/kg p.o. Other representative compounds within this series of diazepinoidolone derivatives include the following:



Compound	R3	R4	A	Isomer	Formula
271130	CO ₂ Me	H	CH	racemic	C ₂₈ H ₂₃ N ₅ O ₄
271131	CO ₂ Me	H	CH	enantiomer B	C ₂₈ H ₂₃ N ₅ O ₄
271132	CO ₂ H	H	CH		C ₂₇ H ₂₁ N ₅ O ₄
271133	H	H	N		C ₂₅ H ₂₀ N ₆ O ₂
271134	H	Cl	CH		C ₂₆ H ₂₀ ClN ₆ O ₂

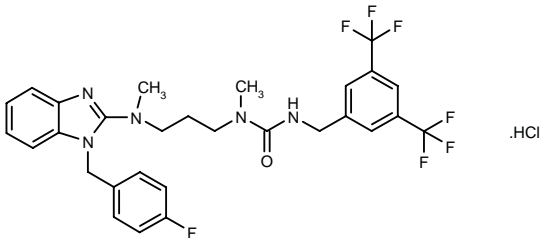
SOURCE – Jouveinal.

REFERENCES

1. Pascal, Y. et al. (Jouveinal SA) *Phosphodiesterase 4-inhibiting diazepinoidolones.* WO 9849169.

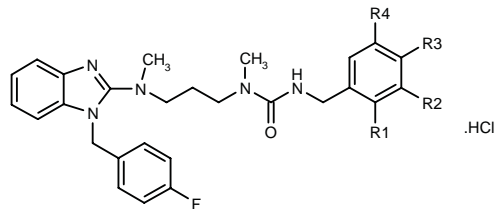
271479

N'-[3,5-Bis(trifluoromethyl)benzyl]-N-[3-[N-[1-(4-fluorobenzyl)benzimidazol-2-yl]-N-methylamino]propyl]-N-methylurea hydrochloride

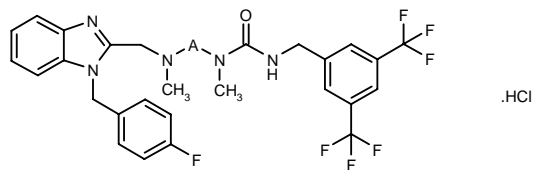


C29 H28 F7 N5 O . HCl; Mol wt: 632.0211

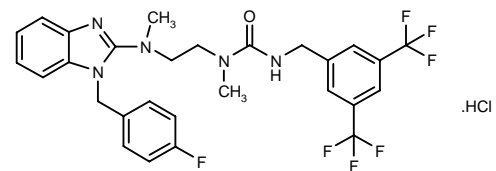
ACTION – Antiallergic, antiasthmatic and antiinflammatory agent with combined substance P-antagonist and antihistaminic activity (IC₅₀ = 0.59 and 0.29 μM, respectively, against substance P- and histamine-induced contractions of guinea pig ileum). A representative compound from a series of benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
271486	OMe	H	H	H	C ₂₈ H ₃₂ FN ₅ O ₂ .HCl
271487	Cl	H	H	H	C ₂₇ H ₂₉ ClFN ₅ O.HCl
271488	H	OMe	OMe	OMe	C ₃₀ H ₃₆ FN ₅ O ₄ .HCl
271490	H	OMe	H	OMe	C ₂₉ H ₃₄ FN ₅ O ₃ .HCl
271491	H	H	F	H	C ₂₇ H ₂₉ F ₂ N ₅ O.HCl
271492	H	H	H	OMe	C ₂₈ H ₃₂ FN ₅ O ₂ .HCl
271494	H	Cl	H	Cl	C ₂₇ H ₂₈ Cl ₂ FN ₅ O.HCl
271495	H	H	OMe	H	C ₂₈ H ₃₂ FN ₅ O ₂ .HCl
271496	H	H	Me	H	C ₂₈ H ₃₂ FN ₅ O.HCl



Compound	A	Formula
271482	-(CH2)3-	C ₃₀ H ₃₀ F ₇ N ₅ O.HCl
271484	-(CH2)2-	C ₂₉ H ₂₈ F ₇ N ₅ O.HCl



271480: C₂₈ H₂₆ F₇ N₅ O . HCl

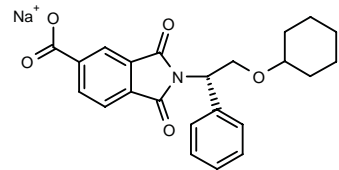
SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Benzimidazole deriv.* WO 9850368.

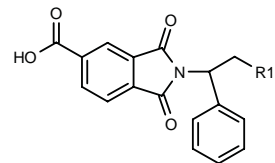
271662

2-[2-(Cyclohexyloxy)-1(*S*)-phenylethyl]-1,3-dioxoisoindoline-5-carboxylic acid sodium salt



C₂₃ H₂₂ N Na O₅ ; Mol wt: 415.4188

ACTION – Antiallergic agent that acts as a selective inhibitor of IgE and IL-5 production. In mouse monocytes stimulated with lipopolysaccharide (LPS), test compound elicited a marked inhibition of IgE production (IC₅₀ = 0.90 μM), with a negligible effect on IgM production (IC₅₀ > 100 μM). Selectivity for IL-5 versus IL-4 was demonstrated *in vitro* in mouse spleen cell preparations stimulated with concanavalin A (ConA), where test compound produced a marked inhibition of IL-5 production (IC₅₀ = 0.10 μM) and a negligible effect on IL-4 production (IC₅₀ > 10 μM). *In vivo* activity was demonstrated by its ability to inhibit IgE production in sensitized mice (ED₃₀ = 50 mg/kg/day x 10 days p.o.), whereas the ED₃₀ value for inhibiting IgM production was > 100 mg/kg. Within this series of phthalamide derivatives, the following are also included:



Compound	R1	Isomer	Formula
271663	cyclohexyl-CH ₂ O	S	C ₂₄ H ₂₅ NO ₅
271664	cyclohexyl-O	S	C ₂₃ H ₂₃ NO ₅
271665	CH ₂ CH ₂ Ph	S	C ₂₅ H ₂₁ NO ₄
271666	CH ₂ CH ₂ Ph	R	C ₂₅ H ₂₁ NO ₄
271667	cyclohexyl-CH ₂	R	C ₂₄ H ₂₅ NO ₄

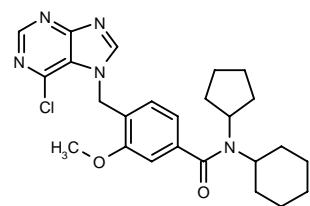
SOURCE – Japan Tobacco.

REFERENCES

1. Kawasaki, H. et al. (Japan Tobacco Inc.) *Phthalamide derivs. and pharmaceutical containing said derivs.* JP 99035559, WO 9852919.

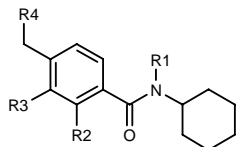
271716

4-(6-Chloro-7*H*-purin-7-ylmethyl)-*N*-cyclohexyl-*N*-cyclopentyl-3-methoxybenzamide



C₂₅ H₃₀ Cl N₅ O₂; Mol wt: 467.9980

ACTION – PAF antagonist, as demonstrated by its ability to inhibit [³H]-PAF binding in human platelet membrane preparations (IC_{50} = 0.077 μ M). Potentially useful for the treatment of asthma, cardiovascular and cerebrovascular disorders, septic shock and the like. Other specifically claimed purinylalkyl benzamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
271717	cyclopentyl	H	OMe	9H-purin-9-yl	C ₂₅ H ₃₁ N ₅ O ₂
271718	cyclopentyl	H	OMe	7H-purin-7-yl	C ₂₅ H ₃₁ N ₅ O ₂
271719	i-Pr	OMe	H	7H-purin-7-yl	C ₂₃ H ₂₉ N ₅ O ₂
271720	i-Pr	OMe	H	7H-purin-7-yl	C ₂₃ H ₂₉ N ₅ O ₂
271721	cyclopentyl	H	OMe	6-Cl-9H-purin-9-yl	C ₂₅ H ₃₀ ClN ₅ O ₂
271722	i-Pr	OMe	H	1H-purin-1-yl	C ₂₃ H ₂₉ N ₅ O ₂
271723	i-Pr	H	H	1H-purin-1-yl	C ₂₂ H ₂₇ N ₅ O

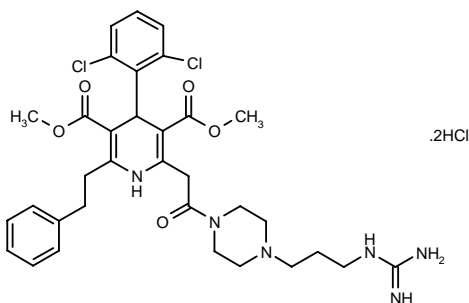
SOURCE – Searle.

REFERENCES

1. Khanna, I.K. and Weier, R.M. (G.D. Searle & Co.) *Purinylalkyl benzamide derivs.* US 5861403.

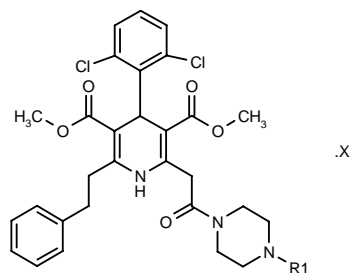
271784

4-(2,6-Dichlorophenyl)-2-[2-[4-(3-guanidinopropyl)-1-piperazinyl]-2-oxoethyl]-6-(2-phenylethyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester dihydrochloride



C33 H40 Cl2 N6 O5 . 2HCl; Mol wt: 744.5438

ACTION – Nonpeptide bradykinin B₂ receptor antagonist with potential in the treatment of inflammation, cardiovascular disorders, pain, the common cold, allergy, asthma, pancreatitis, burns, viral infections, head injury and multiple trauma. Within this series of 1,4-dihydropyridine derivatives, the following are also specifically claimed:



Compound	R1	X	Formula
271785	4,5-dihydro-2-imidazolyl-(CH ₂) ₃	.HCl.HI	C ₃₅ H ₄₁ Cl ₂ N ₅ O ₅ .HCl.HI
271786	4,5-dihydro-2-imidazolyl	HI	C ₃₂ H ₃₅ Cl ₂ N ₅ O ₅ .HI
271787	CH ₂ CH ₂ NHC(=NH)NH ₂	2HCl	C ₃₂ H ₃₈ Cl ₂ N ₆ O ₅ .2HCl

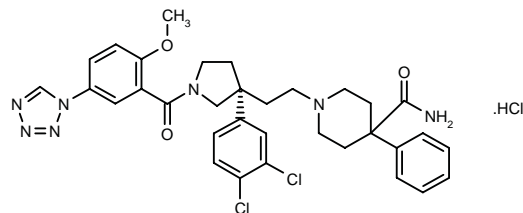
SOURCE – Pfizer.

REFERENCES

1. Ikeda, T. (Pfizer Inc.) *1,4-Dihydropyridine cpds.* US 5861402.

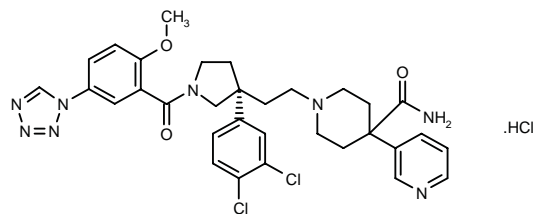
271790

1-[2-[3-(R)-(3,4-Dichlorophenyl)-1-[2-methoxy-5-(1H-tetrazol-1-yl)]benzoyl]pyrrolidin-3-yl]ethyl]-4-phenyl-4-piperidinecarboxamide hydrochloride



C33 H35 Cl2 N7 O3 . HCl; Mol wt: 685.0524

ACTION – Tachykinin receptor antagonist with high affinity for NK₁ (IC_{50} = 2.79 nM) and NK₂ receptors (IC_{50} = 16.3 nM) and improved metabolic stability compared to structurally similar compounds. Claimed for use in the treatment of asthma, cough, bronchitis and pain. Another specifically claimed compound from this series of substituted pyrrolidine derivatives is:



271792: C32 H34 Cl2 N8 O3 . HCl

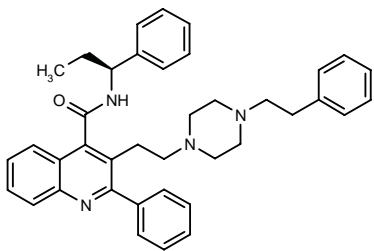
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Burkholder, T.P. et al. (Hoechst Marion Roussel, Inc.) *Heterocyclic subst. pyrrolidine amide derivs.* US 5861417.

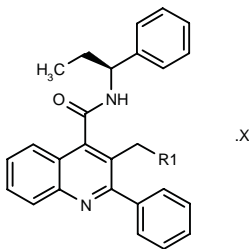
272164

2-Phenyl-3-[2-[4-(2-phenylethyl)piperazin-1-yl]ethyl]-N-[1(S)-phenylpropyl]quinoline-4-carboxamide



C39 H42 N4 O; Mol wt: 582.7878

ACTION – Potent, nonpeptide NK₂ and NK₃ receptor antagonist, as demonstrated in binding studies in CHO cells expressing human NK₂ and NK₃ receptors (K_i = 0.9 and 0.8 nM, respectively). Potentially useful for the treatment of a wide variety of disorders including chronic obstructive pulmonary disease (COPD), asthma, cough, inflammatory bowel disease, psoriasis, rheumatoid arthritis, pain, Crohn’s disease, urinary incontinence, CNS disorders and neurodegenerative disorders. Other exemplified compounds from this series of quinoline-4-carboxamide derivatives include the following:



Compound	R1	X	Formula
272165	4-Ph-1-Piz-CH2CH2	HCl	C ₃₈ H ₄₀ N ₄ O.HCl
272166	4-Ph-1-Pip-CH2CH2		C ₃₉ H ₄₁ N ₃ O
272167	4-PhCH2-1-Piz		C ₃₇ H ₃₈ N ₄ O

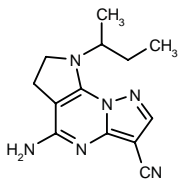
SOURCE – SmithKline Beecham.

REFERENCES

1. Giardina, G.A.M. et al. (SmithKline Beecham SpA) *Quinoline-4-carboxamide derivs. as NK-2 and NK-3 receptor antagonists*. WO 9852942.

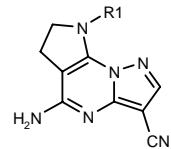
272190

5-Amino-8-(1-methylpropyl)-7,8-dihydro-6H-pyrazolo-[1,5-a]pyrrolo[3,2-e]pyrimidine-3-carbonitrile



C13 H16 N6; Mol wt: 256.3114

ACTION – Bronchodilating agent, proven to inhibit carbachol-, histamine- and LTD₄-induced contractions in guinea pig trachea preparations with pIC₅₀ values of 4.74, 4.81 and 5.43, respectively, compared to respective pIC₅₀ values of 2.53, 3.01 and 3.95 for theophylline. *In vivo*, it was shown to inhibit acetylcholine- and histamine-induced bronchoconstriction in guinea pigs, giving 36.5 and 49.8% inhibition, respectively, at 100 mg/kg administered intragastrically, compared to 39.5 and 37.7% inhibition, respectively, for theophylline at the same dose. A representative compound from a series of tricyclic derivatives, wherein the following are also included:



Compound	R1	Formula
272191	cyclopentyl	C ₁₄ H ₁₆ N ₆
272192	cyclohexyl	C ₁₅ H ₁₈ N ₆

SOURCE – Pola Chemical.

REFERENCES

1. Namiki, T. et al. (Pola Chemical Industries Inc.) *Remedies/preventives for respiratory diseases*. WO 9835968.

sIL-13Rα2-Fc

271414

Soluble IL-13 receptor α2–human IgG Fc fusion protein

ACTION – Soluble IL-13 receptor fusion protein that selectively binds to and neutralizes murine IL-13. In sensitized mice challenged with intratracheal ovalbumin, systemic pretreatment with the fusion protein completely reversed airways hyperresponsiveness.

SOURCE – Genetics Institute.

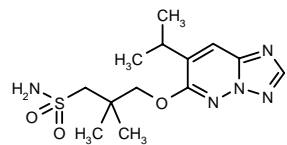
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TAK-661

237094

3-(7-Isopropyl[1,2,4]triazolo[1,5-b]pyridazin-6-yloxy)-2,2-dimethylpropanesulfonamide



C13 H21 N5 O3 S; Mol wt: 327.4069

ACTION – Antiasthmatic agent proven to inhibit both eosinophil chemotaxis (35% inhibition at 10 μ M) and PAF-induced bronchoconstriction in guinea pigs (83% inhibition at 3 mg/kg p.o.).

SOURCE – Takeda.

REFERENCES

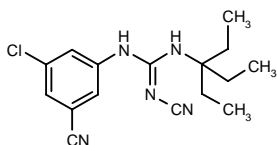
1. Kawano, Y. et al. (Takeda Chemical Industries, Ltd.) *Triazolopyridazines process and intermediates for their preparation and their use as medicaments*. JP 96198878, JP 97328485, WO 9608496.
2. Miyake, A. et al. (Takeda Chemical Industries, Ltd.) *Triazolopyridazines as antiasthmatics*. EP 562439, JP 94279447, US 5389633, US 5482939.
3. Yoshida, K. et al. (Takeda Chemical Industries, Ltd.) *Preparation method of triazolopyridazine derivs*. JP 97216886.
4. Kawano, Y. et al. *Synthesis and pharmacological activity of the novel antiasthmatic agent TAK-661 and related compounds*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-22.
5. Tejima, K. et al. *Specific difference in human and rat metabolism of TAK-661, a novel therapeutic agent for bronchial asthma*. Xenobiotic Metab Dispos 1998, 13(Suppl.): Abst 11P060.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

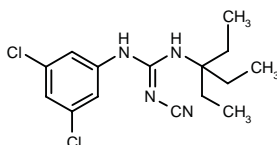
270696

1-(3-Chloro-5-cyanophenyl)-2-cyano-3-(1,1-diethylpropyl)guanidine



C16 H20 Cl N5; Mol wt: 317.8220

ACTION – Potassium channel opener (PCO) with good selectivity for ATP-sensitive potassium channels in vascular smooth muscle (ED_{50} = 94 nM for relaxation of taenia cecum) relative to those in urinary bladder (ED_{50} > 1 μ M for relaxation of urinary bladder) and trachea (ED_{50} = 5.6 μ M for relaxation of trachea). Compound exhibited antihypertensive activity in dogs, reducing mean blood pressure by a maximum of 18.9 ± 2.5 mmHg at a dose of 30 μ g/kg i.v. Another vascular-selective PCO from this series of phenylcyanoguanidine derivatives is:



270697: C15 H20 Cl2 N4

SOURCE – Kanebo.

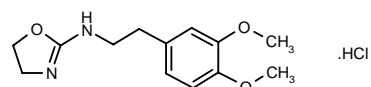
REFERENCES

1. Yoshiizumi, K. et al. *Biologically selective potassium channel openers having 1,1-diethylpropyl group*. Bioorg Med Chem Lett 1998, 8(23): 3397.

270989²

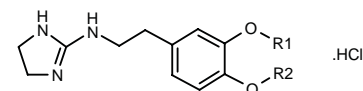
N-[2-(3,4-Dimethoxyphenyl)ethyl]-4,5-dihydrooxazole-2-amine hydrochloride

N-(4,5-Dihydrooxazol-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]amine hydrochloride



C13 H18 N2 O3 . HCl; Mol wt: 286.7571

ACTION – Antihypertensive agent reported to exert marked antihypertensive activity in rats. Other active compounds from this series of imidazoline and oxazoline derivatives are:



Compound	R1	R2	Formula
270990²	Me	Me	C ₁₃ H ₁₈ N ₂ O ₂ .HCl
270991^{1,2}	-CH2-		C ₁₂ H ₁₆ N ₂ O ₂ .HCl

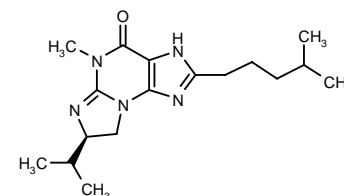
SOURCE – China Pharmaceutical University, Nanjing (CN).

REFERENCES

1. Tatsuno, H. et al. *Synthesis and adrenergic beta-blocking activity of some 1,3-benzodioxole derivatives*. J Med Chem 1977, 20(3): 394.
2. Xu, J.Y. et al. *Synthesis of imidazoline, oxazoline derivatives and antihypertensive activity*. J Chin Pharm Univ 1998, 29(5): 336.

271384

7(*R*)-Isopropyl-5-methyl-2-(4-methylpentyl)-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*b*]purin-4-one



C17 H27 N5 O; Mol wt: 317.4343

ACTION – The most potent inhibitor of the cGMP phosphodiesterases PDE1 and PDE5 (K_i = 12 and 6 nM, respectively) from a series of C-2 alkyl substituted modified tetracyclic guanines with high selectivity relative to PDE3 (K_i = 65,000 nM). Potentially useful for the treatment of cardiovascular disorders.

ACTION – Antiasthmatic agent proven to inhibit both eosinophil chemotaxis (35% inhibition at 10 μ M) and PAF-induced bronchoconstriction in guinea pigs (83% inhibition at 3 mg/kg p.o.).

SOURCE – Takeda.

REFERENCES

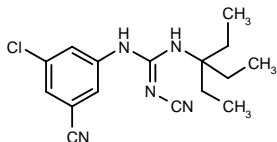
1. Kawano, Y. et al. (Takeda Chemical Industries, Ltd.) *Triazolopyridazines process and intermediates for their preparation and their use as medicaments*. JP 96198878, JP 97328485, WO 9608496.
2. Miyake, A. et al. (Takeda Chemical Industries, Ltd.) *Triazolopyridazines as antiasthmatics*. EP 562439, JP 94279447, US 5389633, US 5482939.
3. Yoshida, K. et al. (Takeda Chemical Industries, Ltd.) *Preparation method of triazolopyridazine derivs*. JP 97216886.
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

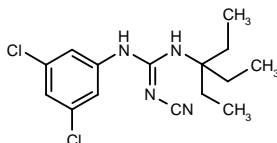
270696

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C16 H20 Cl N5; Mol wt: 317.8220

ACTION – Potassium channel opener (PCO) with good selectivity for ATP-sensitive potassium channels in vascular smooth muscle (ED_{50} = 94 nM for relaxation of taenia cecum) relative to those in urinary bladder (ED_{50} > 1 μ M for relaxation of urinary bladder) and trachea (ED_{50} = 5.6 μ M for relaxation of trachea). Compound exhibited antihypertensive activity in dogs, reducing mean blood pressure by a maximum of 18.9 ± 2.5 mmHg at a dose of 30 μ g/kg i.v. Another vascular-selective PCO from this series of phenylcyanoguanidine derivatives is:



270697: C15 H20 Cl2 N4

SOURCE – Kanebo.

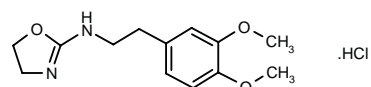
REFERENCES

1. Yoshiizumi, K. et al. *Biologically selective potassium channel openers having 1,1-diethylpropyl group*. Bioorg Med Chem Lett 1998, 8(23): 3397.

270989²

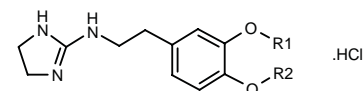
N-[2-(3,4-Dimethoxyphenyl)ethyl]-4,5-dihydrooxazole-2-amine hydrochloride

N-(4,5-Dihydrooxazol-2-yl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]amine hydrochloride



C13 H18 N2 O3 . HCl; Mol wt: 286.7571

ACTION – Antihypertensive agent reported to exert marked antihypertensive activity in rats. Other active compounds from this series of imidazoline and oxazoline derivatives are:



Compound	R1	R2	Formula
270990²	Me	Me	C ₁₃ H ₁₈ N ₂ O ₂ .HCl
270991^{1,2}	-CH2-		C ₁₂ H ₁₆ N ₂ O ₂ .HCl

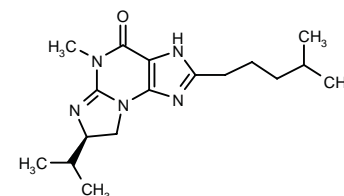
SOURCE – China Pharmaceutical University, Nanjing (CN).

REFERENCES

1. Tatsuno, H. et al. *Synthesis and adrenergic beta-blocking activity of some 1,3-benzodioxole derivatives*. J Med Chem 1977, 20(3): 394.
2. Xu, J.Y. et al. *Synthesis of imidazoline, oxazoline derivatives and antihypertensive activity*. J Chin Pharm Univ 1998, 29(5): 336.

271384

7(*R*)-Isopropyl-5-methyl-2-(4-methylpentyl)-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*b*]purin-4-one



C17 H27 N5 O; Mol wt: 317.4343

ACTION – The most potent inhibitor of the cGMP phosphodiesterases PDE1 and PDE5 (K_i = 12 and 6 nM, respectively) from a series of C-2 alkyl substituted modified tetracyclic guanines with high selectivity relative to PDE3 (K_i = 65,000 nM). Potentially useful for the treatment of cardiovascular disorders.

SOURCE – Schering-Plough.

REFERENCES

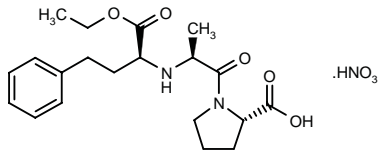
1. Ho, G.D. et al. *Synthesis and evaluation of potent and selective c-GMP phosphodiesterase inhibitors*. Bioorg Med Chem Lett 1999, 9(1): 7.

ENALAPRIL NITRATE

Rec INNM

271805

(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline nitrate



C20 H28 N2 O5 . HNO3; Mol wt: 439.4621

ACTION – Novel salt of enalapril reported to possess improved antihypertensive activity and reduced side effects combined with additional platelet aggregation-inhibitory activity. Compound gave 35 and 67% inhibition of the angiotensin I-induced pressor response in rats at 100 and 300 µg/kg i.p., respectively, being more potent than enalapril maleate (18 and 55% inhibition, respectively, at the same doses). In addition, it exhibited a better respiratory profile than enalapril maleate in a model of bronchospasm induced by substance P in guinea pigs at 100 and 300 µg/kg i.p. Compound was also shown to inhibit collagen-induced platelet aggregation *ex vivo* in rats at 10 mg/kg p.o. (58% inhibition vs. 5% inhibition for enalapril maleate at the same dose). A representative compound from a series of new nitric salts of ACE (angiotensin-converting enzyme) inhibitors.

SOURCE – NicOx.

REFERENCES

1. Del Soldato, P. (NicOx SA) *ACE-inhibitor nitric salts*. WO 9900361.

HUMAN BNP-26

270974

Glycyl-seryl-glycyl-cysteinyl-phenylalanyl-glycyl-arginyl-lysyl-methionyl-aspartyl-arginyl-isoleucyl-seryl-seryl-seryl-glycyl-leucyl-glycyl-cysteinyl-lysyl-valyl-leucyl-arginyl-arginyl-histidine cyclic (S-3.4-S-3.20)-disulfide

C114 H194 N42 O34 S3; Mol wt: 2793.2450

ACTION – Antihypertensive agent with smooth muscle relaxant and diuretic/natriuretic effects. Another exemplified peptide is:

Seryl-prolyl-lysyl-methionyl-valyl-glutaminy-glycyl-seryl-glycyl-cysteinyl-phenylalanyl-glycyl-arginyl-lysyl-methionyl-aspartyl-arginyl-isoleucyl-seryl-seryl-seryl-glycyl-leucyl-glycyl-cysteinyl-lysyl-valyl-leucyl-arginyl-arginyl-histidine cyclic (S-3.10-S-3.26)-disulfide

Human BNP-32 [270975]: C143 H244 N50 O42 S4

SOURCES – Daiichi Pharmaceutical; Daiichi Pure Chemicals.

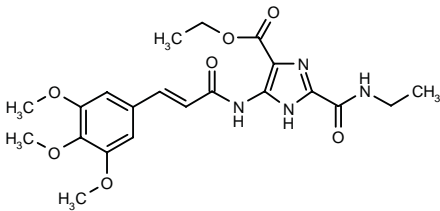
REFERENCES

1. Matsuo, H. et al. (Daiichi Pure Chemicals Co., Ltd.;Daiichi Pharmaceutical Co., Ltd.) *Novel physiologically active peptides and their use*. JP 98310600.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

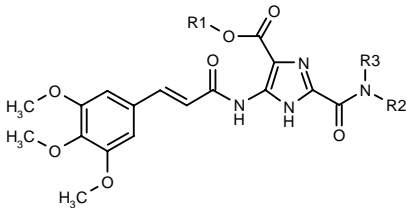
271001

2-(N-Ethylcarbamoyl)-5(4)-[3-(3,4,5-trimethoxyphenyl)-2(E)-propenamido]imidazole-4(5)-carboxylic acid ethyl ester



C21 H26 N4 O7; Mol wt: 446.4574

ACTION – Antiangiogenic agent, an inhibitor of vascular smooth muscle cell proliferation, as demonstrated using thoracic aorta smooth muscle cells from spontaneously hypertensive rats (IC₅₀ = 8 µM). It shows good oral absorption and low acute toxicity (no deaths at up to 1000 mg/kg p.o.) in mice. Within this series of 2-substituted carbamoylimidazole carboxylic acid derivatives, the following are also included:



Compound	R1	R2	R3	Formula
271002	Et	H	Pr	C ₂₂ H ₂₈ N ₄ O ₇
271003	Et	-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₂₃ H ₂₈ N ₄ O ₈
271004	cyclopentyl	H	Pr	C ₂₅ H ₃₂ N ₄ O ₇
271005	4-MeO-Ph-CH ₂ CH ₂	H	Pr	C ₂₉ H ₃₄ N ₄ O ₈
271006	cyclohexyl	H	Me	C ₂₄ H ₃₀ N ₄ O ₇
271007	cyclopentyl	H	Me	C ₂₃ H ₂₈ N ₄ O ₇
271008	CH(CH ₂ OEt) ₂	H	Et	C ₂₆ H ₃₈ N ₄ O ₉

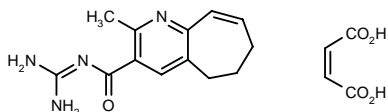
SOURCE – Kissei.

REFERENCES

1. Harada, H. et al. (Kissei Pharmaceutical Co., Ltd.) *2-Substd. carbamoyl-imidazolecarboxylic acid derivs. and vascular-wall thickening inhibitor*. WO 9846573.

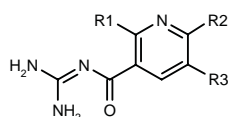
271011

*N*²-(2-methyl-6,7-dihydro-5*H*-cyclohepta[*b*]pyridin-3-ylcarbonyl)guanidine maleate



C₁₃ H₁₆ N₄ O . C₄ H₄ O₄; Mol wt: 360.3680

ACTION – An inhibitor of Na⁺/H⁺ exchange (IC₅₀ < 99 nM in rat platelets) proven to be devoid of toxicity at 100 mg/kg/day i.v. for 5 days in rats. Other representative cycloalka[*b*]pyridine-3-carbonylguanidine derivatives include the following:



Compound	R1	R2,R3	Formula
271012	Me	-CH(OH)(CH ₂) ₃ -	C ₁₂ H ₁₆ N ₄ O ₂
271013	Me	-CH ₂ CH ₂ CH(Me)CH ₂ -	C ₁₃ H ₁₈ N ₄ O
271014	Et	-(CH ₂) ₅ -	C ₁₄ H ₂₀ N ₄ O
271015	Me	-(CH ₂) ₄ CH(OH)-	C ₁₃ H ₁₈ N ₄ O ₂
271016	Me	-CH(Me)(CH ₂) ₄ -	C ₁₄ H ₂₀ N ₄ O
271017	Me	-CH(OMe)(CH ₂) ₄ -	C ₁₄ H ₂₀ N ₄ O ₂
271018	CF ₃	-(CH ₂) ₅ -	C ₁₃ H ₁₅ F ₃ N ₄ O
271019	Cl	-(CH ₂) ₅ -	C ₁₂ H ₁₅ ClN ₄ O
271020	OMe	-(CH ₂) ₅ -	C ₁₃ H ₁₈ N ₄ O ₂
271021	3-Pyr	-(CH ₂) ₅ -	C ₁₇ H ₁₉ N ₅ O

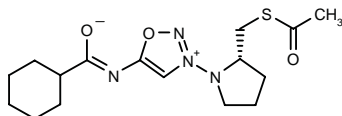
SOURCE – Toa Eiyo.

REFERENCES

1. Takahashi, A. et al. (Toa Eiyo Ltd.) *Cycloalka[b]pyridine-3-carbonylguanidine derivs., process for producing the same, and drugs containing the same.* WO 9839300.

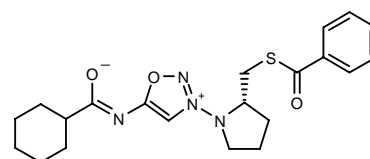
271026

N-[3-[2(*S*)-(Acetylsulfanylmethyl)pyrrolidin-1-yl]-1,2,3-oxadiazolium-5-yl]cyclohexanecarboximate



C₁₆ H₂₄ N₄ O₃ S; Mol wt: 352.4566

ACTION – Agent with vasodilating and platelet aggregation-inhibitory activities intended for use in the treatment of angina pectoris. *In vitro*, compound inhibited arachidonic acid-induced aggregation of rabbit platelet-rich plasma with an IC₅₀ of 4.0 μM (IC₅₀ = 27.5 μM for aspirin), and *in vivo*, it showed blood pressure-lowering activity in rats with an ED₃₀ of 1.4 mg/kg i.d. Another compound from this series of sydnonimine derivatives is:



271027: C₂₁ H₂₆ N₄ O₃ S

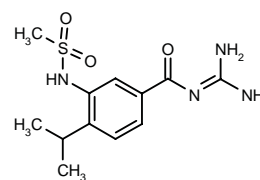
SOURCE – Chugai.

REFERENCES

1. Koga, H. et al. (Chugai Pharmaceutical Co. Ltd.) *Sydnonimine derivs.* JP 99005792, WO 9847896.

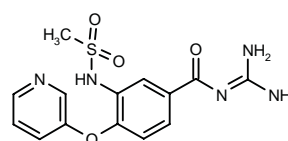
271348

N-[4-Isopropyl-3-(methylsulfonamido)benzoyl]guanidine



C₁₂ H₁₈ N₄ O₃ S; Mol wt: 298.3652

ACTION – Antiischemic agent that acts by inhibiting Na⁺/H⁺ exchange, as demonstrated *in vitro* in rabbit erythrocytes (IC₅₀ = 0.3 μM). Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris, arrhythmias, cardiac and cerebral ischemic disorders, stroke and shock states. Another specifically claimed compound within this series of sulfonylamino-substituted benzoylguanidines is:



271349: C₁₄ H₁₅ N₅ O₄ S

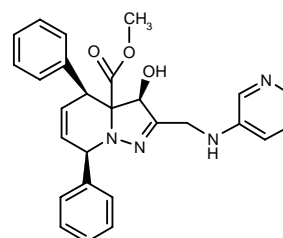
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Kleemann, H.-W. et al. (Hoechst AG) *Sulfonylamino-substd. benzoylguanidines, a process for their preparation, their use as a medicament or diagnostic aid, and medicament containing them.* EP 774459, US 5856344.

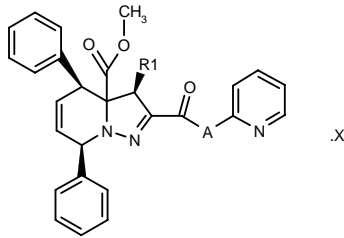
271659

(3*R*,4*S*,7*R*)-3-Hydroxy-4,7-diphenyl-2-(3-pyridinylaminomethyl)-3,3a,4,7-tetrahydropyrazolo[1,5-*a*]pyridine-3a-carboxylic acid methyl ester



C₂₇ H₂₆ N₄ O₃; Mol wt: 454.5274

ACTION – Cardioprotective agent, as demonstrated in an ischemia–reperfusion injury model in rat hearts, with low acute toxicity. Within this series of diazabicyclo compounds, the following are also included:



Compound	R1	A	X	Formula
271660	OH	-(CH2)2-	HCl	C ₂₉ H ₂₇ N ₃ O ₄ ·HCl
271661	NHCH2CH2N(Me)2	-CH2-	2HCl	C ₃₂ H ₃₆ N ₅ O ₃ ·2HCl

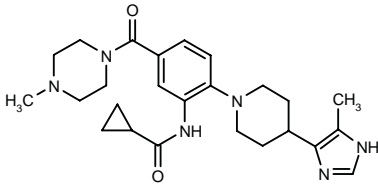
SOURCE – Lederle (Japan).

REFERENCES

1. Matsunaga, H. et al. (Lederle [Japan], Ltd.) *Diazabicyclo cpds.* JP 98287673.

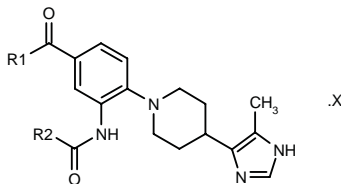
271815

N-[2-[4-(5-Methyl-1*H*-imidazol-4-yl)-1-piperidinyl]-5-(4-methylpiperazin-1-ylcarbonyl)phenyl]cyclopropane-carboxamide



C₂₅ H₃₄ N₆ O₂; Mol wt: 450.5836

ACTION – Na⁺/H⁺ exchange inhibitor with potential in the treatment or prevention of arterial and pulmonary hypertension, cardiac arrhythmia, cardiac ischemia and other ischemic disorders, myocardial infarction, heart failure, angina pectoris, nephropathy, edema, fibrosis and cancer. A representative compound from a series of 4-[(1*H*-imidazol-4-yl)piperidin-1-yl]anilide derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
271816	OMe	Pr		C ₂₁ H ₂₈ N ₄ O ₃
271817	OH	Pr		C ₂₀ H ₂₆ N ₄ O ₃
271818	1-Pip	Pr		C ₂₅ H ₃₅ N ₅ O ₂
271819	NHCH2Ph	Pr		C ₂₇ H ₃₃ N ₅ O ₂
271820	NHCH2CH2N(Me)2	cyclopropyl		C ₂₄ H ₃₄ N ₆ O ₂
271821	NHCH2CH2N(Me)2	1-aziridinyl	HCl	C ₂₃ H ₃₃ N ₇ O ₂ ·HCl

SOURCE – Synthélabo.

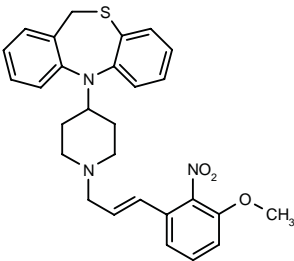
REFERENCES

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ANTIARRHYTHMIC DRUGS

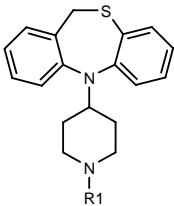
270519

5-[1-[3-(3-Methoxy-2-nitrophenyl)-2(*E*)-propenyl]-4-piperidinyl]-5,11-dihydrodibenzo[*b,e*][1,4]thiazepine



C₂₈ H₂₉ N₃ O₃ S; Mol wt: 487.6211

ACTION – Antiarrhythmic agent whose activity was evaluated in a model of ischemia–reperfusion-induced arrhythmias in rats, where it was found to decrease the incidence of arrhythmia and mortality. Other specifically claimed dibenzothiazepine and dibenzoxazepine derivatives include the following:



Compound	R1	Formula
270520	H	C ₁₈ H ₂₀ N ₂ S
270521	cyclohexyl-(CH2)4	C ₂₈ H ₃₈ N ₂ S
270522	CH2Ph	C ₂₅ H ₂₆ N ₂ S
270523	CH2CH=CHPh	C ₂₇ H ₂₈ N ₂ S
270524	CH2CH2N(<i>i</i> -Pr)2	C ₂₆ H ₃₇ N ₃ S
270525	CH2CH2N(CH2Ph)2	C ₃₄ H ₃₇ N ₃ S
270526	4-Pyr-CH2	C ₂₄ H ₂₅ N ₃ S
270527	CH2CH2CO2Et	C ₂₃ H ₂₈ N ₂ O ₂ S
270528	2-thienyl-CH2	C ₂₃ H ₂₄ N ₂ S ₂
270529	C18H37	C ₃₆ H ₅₆ N ₂ S
270530	CH2CONH2	C ₂₀ H ₂₃ N ₃ OS
270531	4-F-PhCH2	C ₂₅ H ₂₅ FN ₂ S
270532	CH2CH2CO2H	C ₂₁ H ₂₄ N ₂ O ₂ S

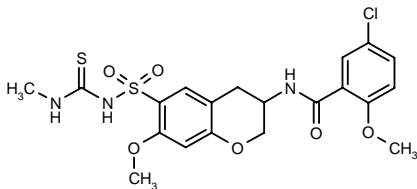
SOURCE – Meiji Seika.

REFERENCES

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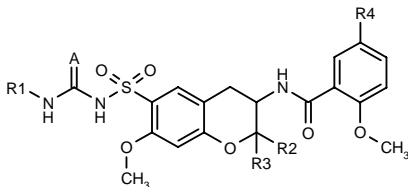
270958

5-Chloro-2-methoxy-*N*-[7-methoxy-6-(*N*'-methylthioureidosulfonyl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-benzamide



C20 H22 Cl N3 O6 S2; Mol wt: 499.9938

ACTION – Antiarrhythmic agent, an inhibitor of ATP-sensitive potassium channels that is able to prolong the action potential duration (APD₉₅: 145 ± 19.1 ms at 2 μM vs. < 40 ms in controls, using guinea pig papillary muscle preparations and rilmakalim as potassium channel opener). It has negligible hypoglycemic activity. Within this series of 3-amidochromanylsulfonyl(thio)urea derivatives, the following are also included:



Compound	R1	R2=R3	R4	A	Formula
270959	Me	H	Cl	O	C ₂₀ H ₂₂ ClN ₃ O ₇ S
270960	Pr	H	Cl	O	C ₂₂ H ₂₆ ClN ₃ O ₇ S
270961	Et	H	Cl	S	C ₂₁ H ₂₄ ClN ₃ O ₆ S ₂
270962	i-Pr	Me	F	S	C ₂₄ H ₃₀ FN ₃ O ₆ S ₂

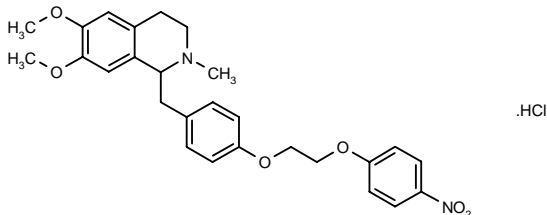
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Englert, H.C. et al. (Hoechst AG) 3-Amidochromanylsulfonyl(thio)ureas, processes for their preparation, their use, and pharmaceutical preparations comprising them. US 5849755.

270995

6,7-Dimethoxy-2-methyl-1-[4-[2-(4-nitrophenoxy)ethoxy]benzyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride



C27 H30 N2 O6 . HCl; Mol wt: 515.0029

ACTION – Antiarrhythmic agent proven to potently inhibit low-KCl-induced contractions of rat aorta and to protect against experimental arrhythmias in rats.

SOURCE – China Pharmaceutical University, Nanjing (CN).

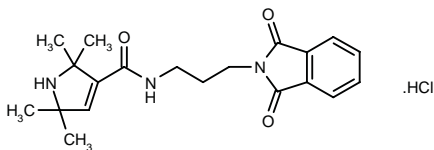
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1. He, L.W. et al. Synthesis and biological activity of 1-(4-alkyloxy)benzyl-1,2,3,4-tetrahydroisoquinolines and related compounds. Acta Pharm Sin 1998, 33(10): 741.

A-2545

248803

N-(3-Phthalimidopropyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide hydrochloride



C20 H25 N3 O3 . HCl; Mol wt: 391.8964

ACTION – Class Ib antiarrhythmic agent that shortens the action potential duration (APD), appears to block both cardiac Na⁺ and Ca²⁺ channels and shows slow binding kinetics. In dogs, compound was able to suppress 24- and 48-h coronary artery ligation-, digitalis-, adrenaline- and programmed electrical stimulation-induced arrhythmias with antiarrhythmic plasma concentrations (IC₅₀) of 1.8, 1.3, 5.8 and 3.7 μg/ml i.v., respectively; it was more potent than mexiletine and showed no arrhythmogenic effects.

SOURCE – Alkaloida.

REFERENCES

1. Hideg, K. et al. (Alkaloida Chem. Fact.) New alkyl diamine derivatives. EP 134225, JP 85500669, US 4703056, US 5028609, US 5032600, WO 8402907.

2. Hankovszky, O.H. et al. New antiarrhythmic agents. 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-tetramethylpyrrolidine-3-carboxamides. (Erratum). J Med Chem 1986, 29(12): 2534.

3. Hankovszky, O.H. et al. New antiarrhythmic agents. 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-tetramethylpyrrolidine-3-carboxamides. J Med Chem 1986, 29(7): 1138.

4. Higashiyama, A. et al. Effect of A-2545, a novel antiarrhythmic agent, on atrioventricular conduction. Folia Pharmacol Jpn 1997, 109(1): Abst 8.

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8. Takacs-Novak, K. and Avdeef, A. Interlaboratory study of log *P* determination by shake-flask and potentiometric methods. J Pharm Biomed Anal 1996, 14(11): 1405.

9. Twomey, P. et al. Direct evidence for in vivo nitroxide free radical production from a new antiarrhythmic drug by EPR spectroscopy. Free Radical Biol Med 1997, 22(5): 909.

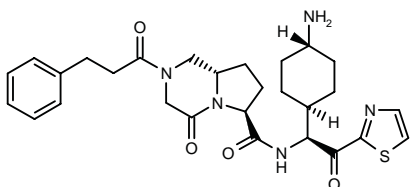
10. Xue, Y.X. et al. Effects of an antiarrhythmic drug A-2545 on canine ventricular arrhythmia models; comparison with mexiletine and flecainide. Naunyn-Schmied Arch Pharmacol 1998, 358(6): 649.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

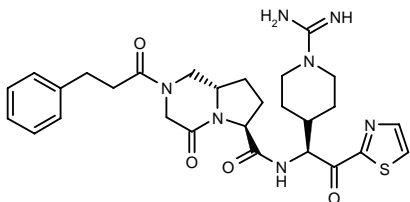
270698

(6*S*,8*aS*)-*N*-[1(*S*)-(trans-4-Aminocyclohexyl)-2-oxo-2-(2-thiazolyl)ethyl]-4-oxo-2-(3-phenylpropanoyl)octahydropyrrolo[1,2-*a*]pyrazine-6-carboxamide



C28 H35 N5 O4 S; Mol wt: 537.6815

ACTION – Potent and selective thrombin inhibitor (IC_{50} = 33 nM against human thrombin) with 270-fold selectivity over human trypsin. In a rat arterial thrombosis model, it exhibited good anticoagulant and antithrombotic activity after i.v. but not oral administration. Another nonpeptide bicyclic lactam inhibitor with a similar profile is:



271355: C28 H35 N7 O4 S

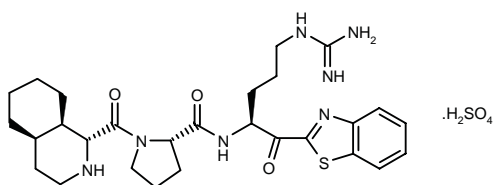
SOURCES – BioChem Pharma; Warner-Lambert.

REFERENCES

1. Plummer, J.S. et al. *Potent and selective bicyclic lactam inhibitors of thrombin: Part 2: P1 modifications*. Bioorg Med Chem Lett 1998, 8(23): 3409.

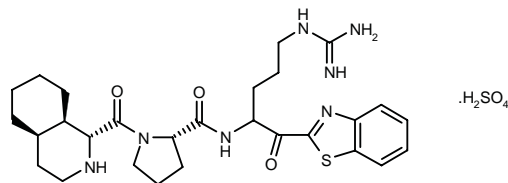
271375

2-[*N*-[(1*R*,4*aR*,8*aR*)-Perhydroisoquinolin-1-ylcarbonyl]-L-prolyl-L-arginyl]benzothiazole sulfate



C28 H39 N7 O3 S . H2 O4 S; Mol wt: 651.8059

ACTION – Antithrombotic agent that acts by inhibiting both thrombin and factor Xa, proven to possess anticoagulant and antithrombotic activity in several *in vitro* and *in vivo* experimental models. For example, it gave an ED_{50} (dose reducing thrombus weight by 50%) of 0.008 mg/kg/h i.v. in the rabbit arteriovenous (AV) shunt model. Another specifically claimed compound is:



271376: C28 H39 N7 O3 S . H2 O4 S

SOURCE – Lilly.

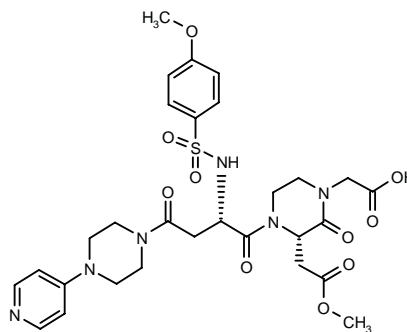
REFERENCES

1. Jackson, C.V. et al. (Eli Lilly and Company) *Antithrombotic cpd*. WO 9851684.

ANTIPLATELET THERAPY

271198

2-[3(*S*)-(Methoxycarbonylmethyl)-4-[2(*S*)-(4-methoxyphenylsulfonamido)-4-[4-(4-pyridinyl)piperazin-1-yl]-succinyl]-2-oxopiperazin-1-yl]acetic acid



C29 H36 N6 O10 S; Mol wt: 660.7014

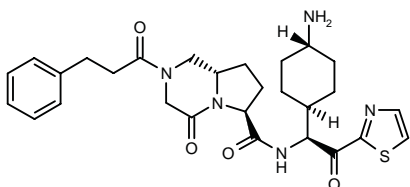
ACTION – Platelet aggregation inhibitor that acts by virtue of its fibrinogen (gpIIb/IIIa) receptor-antagonist activity. Claimed for use in the treatment or prevention of angina pectoris, unstable angina, ischemic complications, and restenosis or reobstruction following angioplasty or thrombolytic therapy. A specifically claimed compound within a series of 2-oxopiperazin-1-acetic acid derivatives, wherein the following are also included:

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

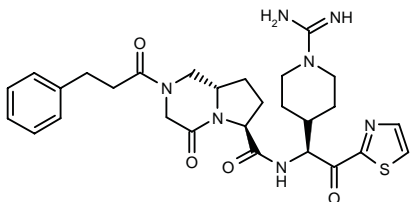
270698

(6*S*,8*aS*)-*N*-[1(*S*)-(trans-4-Aminocyclohexyl)-2-oxo-2-(2-thiazolyl)ethyl]-4-oxo-2-(3-phenylpropanoyl)octahydropyrrolo[1,2-*a*]pyrazine-6-carboxamide



C28 H35 N5 O4 S; Mol wt: 537.6815

ACTION – Potent and selective thrombin inhibitor (IC_{50} = 33 nM against human thrombin) with 270-fold selectivity over human trypsin. In a rat arterial thrombosis model, it exhibited good anticoagulant and antithrombotic activity after i.v. but not oral administration. Another nonpeptide bicyclic lactam inhibitor with a similar profile is:



271355: C28 H35 N7 O4 S

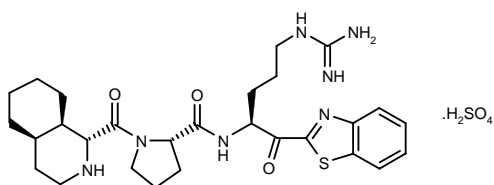
SOURCES – BioChem Pharma; Warner-Lambert.

REFERENCES

1. Plummer, J.S. et al. *Potent and selective bicyclic lactam inhibitors of thrombin: Part 2: P1 modifications*. Bioorg Med Chem Lett 1998, 8(23): 3409.

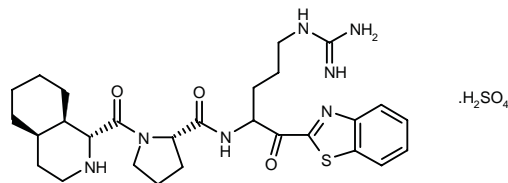
271375

2-[*N*-[(1*R*,4*aR*,8*aR*)-Perhydroisoquinolin-1-ylcarbonyl]-L-prolyl-L-arginyl]benzothiazole sulfate



C28 H39 N7 O3 S . H2 O4 S; Mol wt: 651.8059

ACTION – Antithrombotic agent that acts by inhibiting both thrombin and factor Xa, proven to possess anticoagulant and antithrombotic activity in several *in vitro* and *in vivo* experimental models. For example, it gave an ED_{50} (dose reducing thrombus weight by 50%) of 0.008 mg/kg/h i.v. in the rabbit arteriovenous (AV) shunt model. Another specifically claimed compound is:



271376: C28 H39 N7 O3 S . H2 O4 S

SOURCE – Lilly.

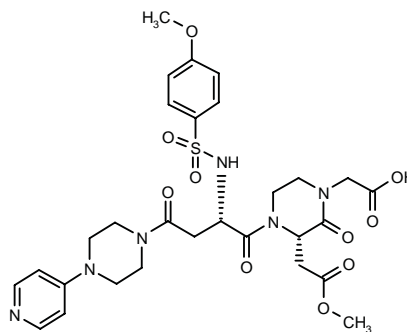
REFERENCES

1. Jackson, C.V. et al. (Eli Lilly and Company) *Antithrombotic cpd*. WO 9851684.

ANTIPLATELET THERAPY

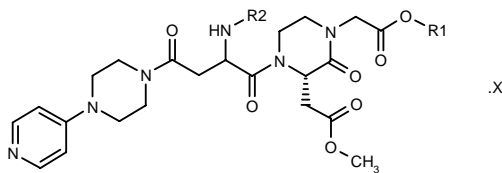
271198

2-[3(*S*)-(Methoxycarbonylmethyl)-4-[2(*S*)-(4-methoxyphenylsulfonamido)-4-[4-(4-pyridinyl)piperazin-1-yl]-succinyl]-2-oxopiperazin-1-yl]acetic acid

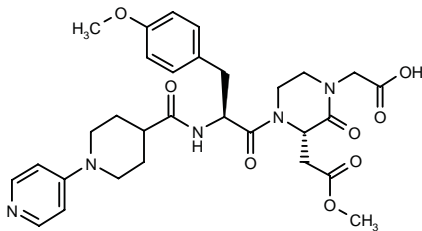


C29 H36 N6 O10 S; Mol wt: 660.7014

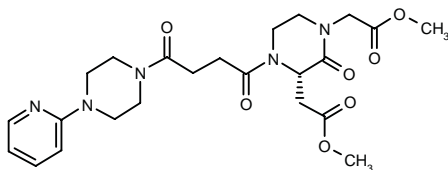
ACTION – Platelet aggregation inhibitor that acts by virtue of its fibrinogen (gpIIb/IIIa) receptor-antagonist activity. Claimed for use in the treatment or prevention of angina pectoris, unstable angina, ischemic complications, and restenosis or reobstruction following angioplasty or thrombolytic therapy. A specifically claimed compound within a series of 2-oxopiperazin-1-acetic acid derivatives, wherein the following are also included:



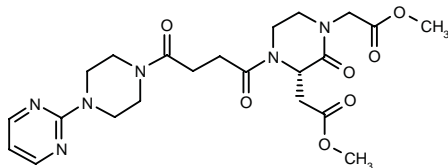
Compound	R1	R2	Isomer	X	Formula
271200	H	4-MeO-PhCH2	S		C ₃₀ H ₃₈ N ₆ O ₈
271207	t-Bu	t-BuOCO	S		C ₃₁ H ₄₆ N ₆ O ₉
271208	H	CO2Me	S	HCl	C ₂₄ H ₃₂ N ₆ O ₉ .HCl
271209	H	4-MeO-PhSO2	R	CF3CO2H	C ₂₉ H ₃₆ N ₆ O ₁₀ S.C ₂ HF ₃ O ₂
271212	H	Me	R		C ₂₃ H ₃₂ N ₆ O ₇
271213	H	t-BuCO2-CH2OCO	R	HCl	C ₂₉ H ₄₀ N ₆ O ₁₁ .HCl



271203: C30 H37 N5 O8



271204: C23 H31 N5 O7



271205: C22 H30 N6 O7

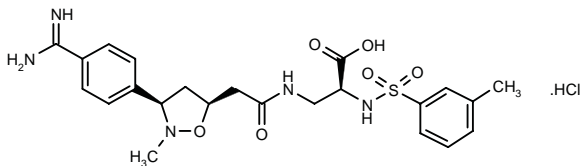
SOURCE – Takeda.

REFERENCES

1. Tamura, N. and Terashita, Z. (Takeda Chemical Industries, Ltd.) *2-Piperazinone-1-acetic acid derivs. and their use.* JP 98306092, WO 9839324.

271391

3-[3(R)-(4-Carbamimidoylphenyl)-2-methylisoxazolidin-5(S)-ylacetamido]-2(S)-(3-methylphenylsulfonamido)-propionic acid hydrochloride



C23 H29 N5 O6 S . HCl; Mol wt: 540.0380

ACTION – Platelet aggregation inhibitor from a series of RGD-mimic isoxazolidines, a highly potent fibrinogen (gpIIb/IIIa) receptor antagonist; it inhibited ADP-induced human platelet aggregation with an IC₅₀ of 28 nM. *Ex vivo* in dogs, compound administered at a dose of 0.025 mg/kg i.v. provided potent (over 50%) and long-lasting (12 h) inhibition of platelet aggregation.

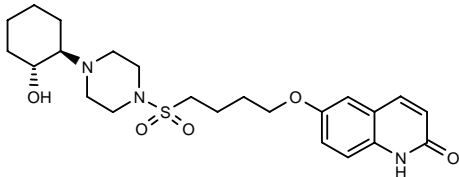
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Confalone, P.N. et al. *Platelet glycoprotein IIb/IIIa receptor antagonists derived from isoxazolidines.* Bioorg Med Chem Lett 1999, 9(1): 55.

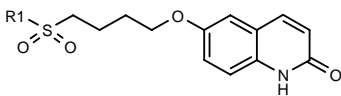
271686

trans-6-[4-[4-(2-Hydroxycyclohexyl)piperazin-1-ylsulfonyl]butoxy]quinolin-2(1H)-one



C23 H33 N3 O5 S; Mol wt: 463.5957

ACTION – Antithrombotic and antiatherosclerotic agent that displays marked platelet aggregation-inhibitory activity in studies using rabbit platelets and ADP and collagen as agonists (IC₅₀ = 1.68 and 1.05 μM, respectively). *In vivo*, the compound produced 93% inhibition of collagen-induced pulmonary embolism in mice at a dose of 30 mg/kg p.o. In addition, it exhibited significant inhibitory activity on vascular intimal hypertrophy induced by balloon injury of the rat left common carotid artery: 28.2% inhibition at 30 mg/kg b.i.d. p.o. Within this series of carbostyryl derivatives, the following are also included:



Compound	R1	Formula
271687	4-PhCH2-1-Piz	C ₂₄ H ₂₉ N ₃ O ₄ S
271688	4-(cyclopropyl)-1-Piz	C ₂₀ H ₂₇ N ₃ O ₄ S
271689	trans-4-(2-AcO-cyclohexyl)-1-Piz	C ₂₅ H ₃₅ N ₃ O ₆ S
271691	8aS-perhydropyrrolo[1,2-a]pyrazin-2-yl	C ₂₀ H ₂₇ N ₃ O ₄ S
271692	2(S)-(AcOCH2)-1-pyrrolidinyl	C ₂₀ H ₂₆ N ₂ O ₆ S
271693	4-morpholinyl	C ₁₇ H ₂₂ N ₂ O ₅ S

SOURCE – Otsuka.

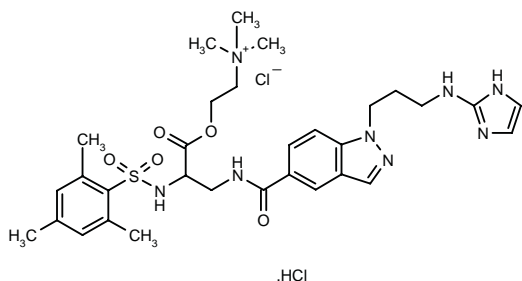
REFERENCES

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SD-209

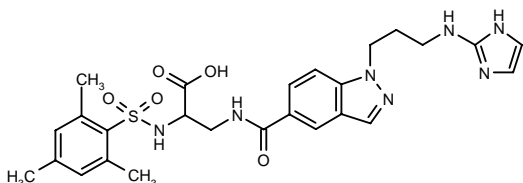
271422

2-[3-[1-[3-(1*H*-imidazol-2-ylamino)propyl]-1*H*-indazol-5-ylcarboxamido]-2-[2,4,6-(trimethyl)phenylsulfonamido]-propionyloxy]-*N,N,N*-trimethyl-1-ethanaminium chloride hydrochloride



C31 H43 Cl N8 O5 S . HCl; Mol wt: 711.7116

ACTION – Integrin inhibitor prodrug that is transformed to the active compound **SM-256**, which then inhibits cell adhesion via its antagonist activity at the vitronectin ($\alpha_v\beta_3$) receptor. Claimed for use in the treatment of thrombosis, osteoporosis, angiogenic disorders, retinopathy, restenosis and metastatic disorders.



SM-256 [271423]: C26 H31 N7 O5 S

SOURCE – DuPont Pharmaceuticals.

REFERENCES

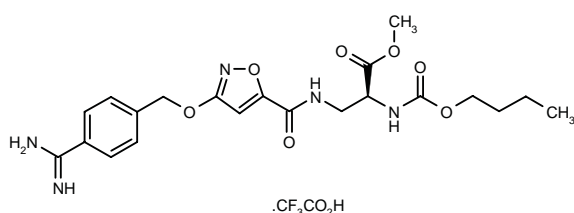
- Jadhav, P. et al. (DuPont Pharmaceuticals Co.) *Heterocyclic integrin inhibitor prodrugs*. WO 9843962.

XU-065*

271177

228068 (as free base)

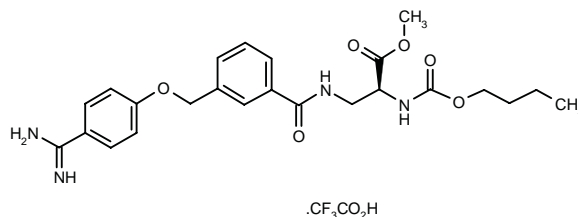
3-[3-(4-Amidinobenzoyloxy)isoxazol-5-ylcarboxamido]-2(*R*)-(butoxycarbonylamino)propionic acid methyl ester trifluoroacetate



C21 H27 N5 O7 . C2 H F3 O2; Mol wt: 575.4942

ACTION – Orally active antiplatelet agent, a potent fibrinogen (gpIIb/IIIa) receptor antagonist proven to inhibit ADP-induced human platelet aggregation with an IC₅₀ of 50 ± 7 nM. After oral administration, compound dose-dependently (0.5-1.6 mg/kg) inhibited *ex vivo*

ADP-induced platelet aggregation in dogs, with maximal inhibition maintained for 5 h following the highest dose. Another chemically related compound from the isoxazole series is:



XU-057 [271178]: C24 H30 N4 O6 . C2 H F3 O2

SOURCE – DuPont Pharmaceuticals.

REFERENCES

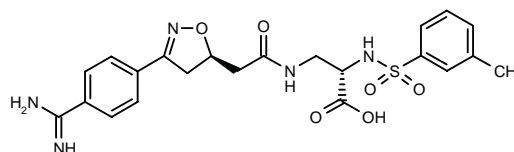
- Degrado, W.F. and Xue, C.-B. (The Du Pont Merck Pharmaceutical Co.) *Cpds. containing basic and acidic termini useful as fibrinogen receptor antagonists*. US 5563158, WO 9518111.
- Xue, C.-B. et al. *Synthesis and antiplatelet effects of an isoxazole series of glycoprotein IIb/IIIa antagonists*. Bioorg Med Chem Lett 1998, 8(24): 3499.

*Identified compound **228068** (see **226586**) Drug Data Report 1995, 017(11): 1007.

XV-454

256548

3-[2-[3-(4-Carbamimidoylphenyl)-4,5-dihydroisoxazol-5(*R*)-yl]acetamido]-2(*S*)-(3-methylphenylsulfonamido)-propionic acid



C22 H25 N5 O6 S; Mol wt: 487.5345

ACTION – Nonpeptide antiplatelet agent, a potent fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 10 nM against [³H]-fibrinogen binding in activated human platelets) with high selectivity relative to vitronectin receptors (IC₅₀ > 10 μM); it showed similar affinity for both activated and unactivated human platelets and relatively slow dissociation rates. Compound potently inhibited human platelet aggregation induced by ADP, thrombin receptor agonist peptide (TRAP) or collagen (IC₅₀ = 14-25 nM). In baboons, oral (0.1 mg/kg) and i.v. infusion (0.05 mg/kg/30 min) administration produced 60-80 and 100% inhibition of platelet aggregation, respectively, which was sustained for 48-72 h; it also produced significant but reversible prolongation of bleeding time, without any significant effect on platelet count, clinical chemistry or hemodynamic parameters.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

- Wityak, J. et al. (The Du Pont Merck Pharmaceutical Co.) *Novel isoxazoline and isoxazole fibrinogen receptor antagonists*. EP 730590, EP 832076, JP 97505590, US 5849736, WO 9514683, WO 9638426.
- Mousa, S.A. et al. *XV454, a novel non-peptide antiplatelet agent with comparable platelet αIIbβ3 binding kinetics to c7E3 and long lasting antiplatelet efficacy after single intravenous or oral administration in non-human primates*. Circulation 1997, 96(8, Suppl.): Abstr 928.

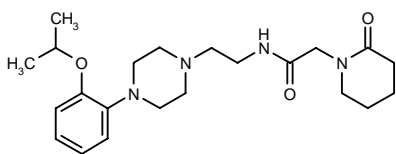
3. Mousa, S.A. et al. *XV454, a novel nonpeptide small-molecule platelet GIIb/IIIa antagonist with comparable platelet α IIb β 3-binding kinetics to c7E3*. *J Cardiovasc Pharmacol* 1998, 32(5): 736.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

271338

N-[2-[4-(2-Isopropoxyphenyl)piperazin-1-yl]ethyl]-2-(2-oxopiperidin-1-yl)acetamide



C22 H34 N4 O3; Mol wt: 402.5356

ACTION – Agent for the treatment of benign prostatic hyperplasia, an α_1 -adrenoceptor antagonist with selectivity for the α_{1a} subtype (IC_{50} = 8.7 nM) over α_{1b} (IC_{50} = 46,120 nM) and α_{1d} (IC_{50} = 372 nM) subtypes. In a functional assay, it exhibited an IC_{50} value of 99 μ M for inhibition of norepinephrine-induced mobilization of cytosolic calcium in HEK-293s cells expressing the human α_{1a} -adrenoceptor; in addition, it exhibited IC_{50} values of 1.3 and 31.9 μ M, respectively, for inhibition of norepinephrine-induced contractions in rat prostate and rat aorta, thus showing selectivity for prostatic over aortic tissue. *In vivo*, compound was found to inhibit phenylephrine-induced increases in intraurethral pressure in dogs at 3-300 μ g/kg i.v., while showing little effect on mean arterial pressure. A representative compound from a series of aryl-substituted piperazines.

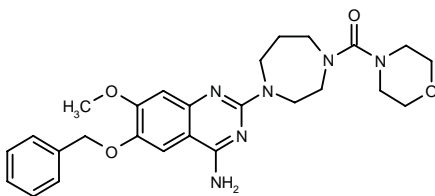
SOURCE – Ortho-McNeil.

REFERENCES

1. Jolliffe, L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Arylsubstd. piperazines useful in the treatment of benign prostatic hyperplasia*. WO 9851298.

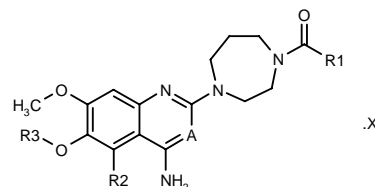
271451

1-[4-[4-Amino-6-(benzyloxy)-7-methoxy-2-quinazolinyl]-perhydro-1,4-diazepin-1-yl]-1-(4-morpholinyl)methanone



C26 H32 N6 O4; Mol wt: 492.5768

ACTION – Agent for the treatment of benign prostatic hyperplasia reported to be devoid of cardiovascular side effects due to its selective antagonism of prostatic α_1 -adrenoceptors. Within this series of quinolines and quinazolines, the following are also included:



Compound	R1	R2	R3	A	X	Formula
271452	4-morpholinyl	H	4-F-Ph-CH2	N	HCl	C ₂₆ H ₃₁ N ₅ O ₄ .HCl
271453	2-THF	H	CH2Ph	N		C ₂₆ H ₃₁ N ₅ O ₄
271454	4-morpholinyl	cyclobutyl-O	Me	N		C ₂₄ H ₃₄ N ₆ O ₅
271455	4-morpholinyl	cyclobutyl-O	Me	CH		C ₂₅ H ₃₅ N ₅ O ₅
271456	4-morpholinyl	OCH2CF3	Me	CH		C ₂₃ H ₃₀ F ₃ N ₅ O ₅

SOURCE – Pfizer.

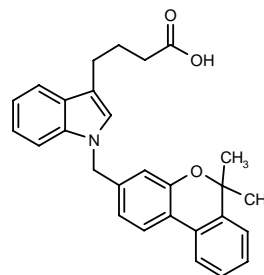
REFERENCES

1. Fox, D.N.A. et al. (Pfizer Ltd.;Pfizer Inc.) *Quinolines and quinazolines useful in therapy*. EP 887344, JP 99012274.

FR-119680

270366

4-[1-(6,6-Dimethyl-6*H*-dibenzo[*b,d*]pyran-3-yl)methyl]-1*H*-indol-3-yl]butanoic acid



C28 H27 N O3; Mol wt: 425.5253

ACTION – Nonsteroidal 5 α -reductase inhibitor with potent *in vitro* activity against rat prostatic 5 α -reductase (IC_{50} = 5.0 nM). *In vivo*, at a dose of 10 mg/kg s.c. for 5 days it reduced prostate weight of young testosterone-treated castrated rats by 44.1%. Prototype compound from a series of 1-benzylindole-3-alkanoic acids with potential for the treatment of the benign prostatic hyperplasia (BPH).

SOURCE – Fujisawa.

REFERENCES

1. Sawada, K. et al. (1-Benzylindole-3-yl)-alkanoic acids; novel nonsteroidal inhibitors of steroid 5 α -reductase (I). *Chem Pharm Bull* 1998, 46(11): 1683.

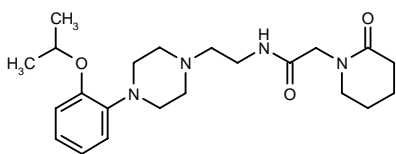
3. Mousa, S.A. et al. *XV454, a novel nonpeptide small-molecule platelet GIIb/IIIa antagonist with comparable platelet α IIb β 3-binding kinetics to c7E3*. *J Cardiovasc Pharmacol* 1998, 32(5): 736.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

271338

N-[2-[4-(2-Isopropoxyphenyl)piperazin-1-yl]ethyl]-2-(2-oxopiperidin-1-yl)acetamide



C22 H34 N4 O3; Mol wt: 402.5356

ACTION – Agent for the treatment of benign prostatic hyperplasia, an α_1 -adrenoceptor antagonist with selectivity for the α_{1a} subtype (IC_{50} = 8.7 nM) over α_{1b} (IC_{50} = 46,120 nM) and α_{1d} (IC_{50} = 372 nM) subtypes. In a functional assay, it exhibited an IC_{50} value of 99 μ M for inhibition of norepinephrine-induced mobilization of cytosolic calcium in HEK-293s cells expressing the human α_{1a} -adrenoceptor; in addition, it exhibited IC_{50} values of 1.3 and 31.9 μ M, respectively, for inhibition of norepinephrine-induced contractions in rat prostate and rat aorta, thus showing selectivity for prostatic over aortic tissue. *In vivo*, compound was found to inhibit phenylephrine-induced increases in intraurethral pressure in dogs at 3-300 μ g/kg i.v., while showing little effect on mean arterial pressure. A representative compound from a series of aryl-substituted piperazines.

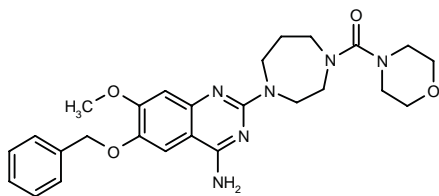
SOURCE – Ortho-McNeil.

REFERENCES

1. Jolliffe, L. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Arylsubstd. piperazines useful in the treatment of benign prostatic hyperplasia*. WO 9851298.

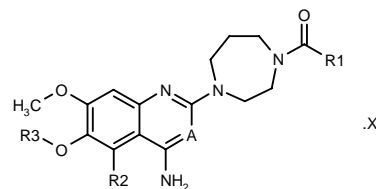
271451

1-[4-[4-Amino-6-(benzyloxy)-7-methoxy-2-quinazolinyl]-perhydro-1,4-diazepin-1-yl]-1-(4-morpholinyl)methanone



C26 H32 N6 O4; Mol wt: 492.5768

ACTION – Agent for the treatment of benign prostatic hyperplasia reported to be devoid of cardiovascular side effects due to its selective antagonism of prostatic α_1 -adrenoceptors. Within this series of quinolines and quinazolines, the following are also included:



Compound	R1	R2	R3	A	X	Formula
271452	4-morpholinyl	H	4-F-Ph-CH2	N	HCl	C ₂₆ H ₃₁ FN ₅ O ₄ .HCl
271453	2-THF	H	CH2Ph	N		C ₂₆ H ₃₁ N ₅ O ₄
271454	4-morpholinyl	cyclobutyl-O	Me	N		C ₂₄ H ₃₄ N ₆ O ₅
271455	4-morpholinyl	cyclobutyl-O	Me	CH		C ₂₅ H ₃₅ N ₅ O ₅
271456	4-morpholinyl	OCH2CF3	Me	CH		C ₂₃ H ₃₀ F ₃ N ₅ O ₅

SOURCE – Pfizer.

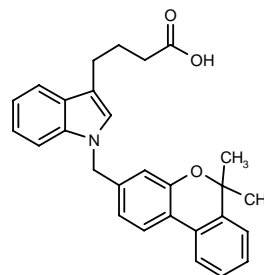
REFERENCES

1. Fox, D.N.A. et al. (Pfizer Ltd.;Pfizer Inc.) *Quinolines and quinazolines useful in therapy*. EP 887344, JP 99012274.

FR-119680

270366

4-[1-(6,6-Dimethyl-6*H*-dibenzo[*b,d*]pyran-3-yl)methyl]-1*H*-indol-3-yl]butanoic acid



C28 H27 N O3; Mol wt: 425.5253

ACTION – Nonsteroidal 5 α -reductase inhibitor with potent *in vitro* activity against rat prostatic 5 α -reductase (IC_{50} = 5.0 nM). *In vivo*, at a dose of 10 mg/kg s.c. for 5 days it reduced prostate weight of young testosterone-treated castrated rats by 44.1%. Prototype compound from a series of 1-benzylindole-3-alkanoic acids with potential for the treatment of the benign prostatic hyperplasia (BPH).

SOURCE – Fujisawa.

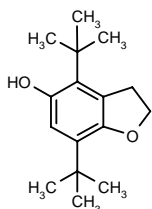
REFERENCES

1. Sawada, K. et al. (1-Benzylindole-3-yl)-alkanoic acids; novel nonsteroidal inhibitors of steroid 5 α -reductase (I). *Chem Pharm Bull* 1998, 46(11): 1683.

TREATMENT OF RENAL DISEASES

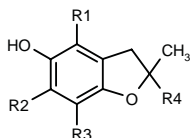
271463

4,7-Di-*tert*-butyl-2,3-dihydro-1-benzofuran-5-ol



C16 H24 O2; Mol wt: 248.3636

ACTION – Agent for the treatment or prevention of renal disorders and for organ preservation, proven to protect porcine kidney-derived LLC-PK1 cells and cultured mesangial cells from LDL-induced oxidation at concentrations 0.1-10 and 1-3 μ M, respectively. Other compounds from this series of 2,3-dihydrobenzofuran derivatives include the following:



Compound	R1	R2	R3	R4	Formula
271464	t-Bu	H	t-Bu	H	C ₁₇ H ₂₆ O ₂
271465	H	t-Bu	H	Me	C ₁₄ H ₂₀ O ₂

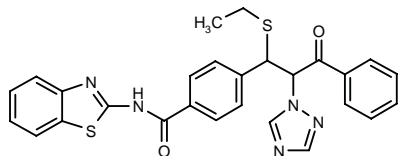
SOURCE – Chugai.

REFERENCES

1. Ishikawa, A. et al. (Chugai Pharmaceutical Co. Ltd.) *2,3-Dihydrobenzofuran derivs.* JP 99035568, WO 9852557.

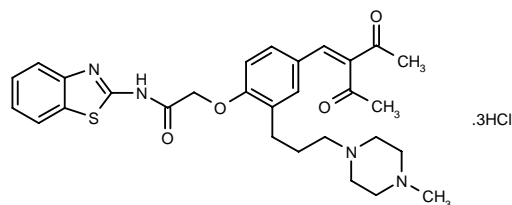
271677

N-(2-Benzothiazolyl)-4-[1-(ethylsulfanyl)-2-benzoyl-2-(1,2,4-triazol-1-yl)ethyl]benzamide



C27 H23 N5 O2 S2; Mol wt: 513.6437

ACTION – Protein kinase C (PKC) inhibitor (IC_{50} = 0.4 μ M using enzyme purified from rat brain) proven active in a model of renal failure induced by ischemia–reperfusion in rats, significantly decreasing blood urea nitrogen and serum creatinine levels at 10 and 100 mg/kg p.o. Another exemplified compound is:



271678: C29 H34 N4 O4 S . 3HCl

SOURCE – Otsuka.

REFERENCES

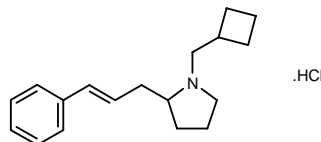
1. Mori, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzene derivs.* JP 98287634.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

270946

1-(Cyclobutylmethyl)-2-[3-phenyl-2(*E*)-propenyl]-pyrrolidine hydrochloride



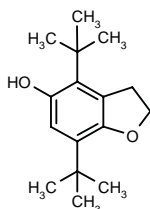
C18 H25 N . HCl ; Mol wt: 291.8634

ACTION – Agent for the treatment of gastrointestinal and psychotic disorders, particularly ulcers, that acts by antagonizing σ -receptors, with a potency comparable or slightly higher than that of haloperidol (IC_{50} = 4.52 and 8.95 nM, respectively, using brain membrane preparations and [³H]-SK&F-10047 as the ligand). In contrast to haloperidol, test compound showed negligible affinity for phencyclidine (PCP) receptors (IC_{50} >10,000 nM vs. 1.268 nM for haloperidol). *In vivo*, compound was effective in inhibiting cysteamine-induced ulcers in rats and it was 50-60 times more active than the known compound igmesine (ED_{50} = 0.137 and 5.950 mg/kg i.p., respectively). In addition, the compound protected against diarrhea induced experimentally by the bacterial endotoxin *Salmonella* lipopolysaccharide, with an ED_{50} value below 100 μ g/kg p.o. It had negligible acute toxicity in rats. Within this series of 2-(arylalkenyl)azacycloalkane derivatives, the following are also included:

TREATMENT OF RENAL DISEASES

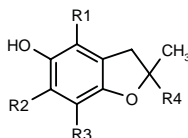
271463

4,7-Di-*tert*-butyl-2,3-dihydro-1-benzofuran-5-ol



C16 H24 O2; Mol wt: 248.3636

ACTION – Agent for the treatment or prevention of renal disorders and for organ preservation, proven to protect porcine kidney-derived LLC-PK1 cells and cultured mesangial cells from LDL-induced oxidation at concentrations 0.1-10 and 1-3 μ M, respectively. Other compounds from this series of 2,3-dihydrobenzofuran derivatives include the following:



Compound	R1	R2	R3	R4	Formula
271464	t-Bu	H	t-Bu	H	C ₁₇ H ₂₆ O ₂
271465	H	t-Bu	H	Me	C ₁₄ H ₂₀ O ₂

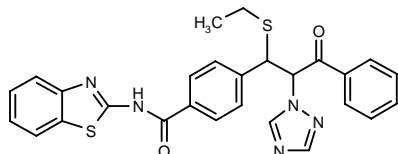
SOURCE – Chugai.

REFERENCES

1. Ishikawa, A. et al. (Chugai Pharmaceutical Co. Ltd.) *2,3-Dihydrobenzofuran derivs.* JP 99035568, WO 9852557.

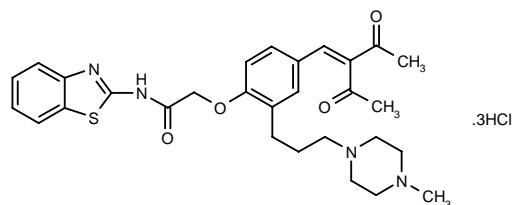
271677

N-(2-Benzothiazolyl)-4-[1-(ethylsulfanyl)-2-benzoyl-2-(1,2,4-triazol-1-yl)ethyl]benzamide



C27 H23 N5 O2 S2; Mol wt: 513.6437

ACTION – Protein kinase C (PKC) inhibitor (IC_{50} = 0.4 μ M using enzyme purified from rat brain) proven active in a model of renal failure induced by ischemia–reperfusion in rats, significantly decreasing blood urea nitrogen and serum creatinine levels at 10 and 100 mg/kg p.o. Another exemplified compound is:



271678: C29 H34 N4 O4 S . 3HCl

SOURCE – Otsuka.

REFERENCES

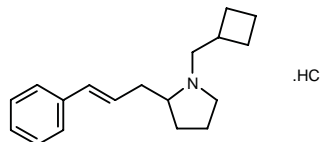
1. Mori, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzene derivs.* JP 98287634.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

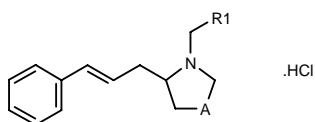
270946

1-(Cyclobutylmethyl)-2-[3-phenyl-2(*E*)-propenyl]-pyrrolidine hydrochloride



C18 H25 N . HCl ; Mol wt: 291.8634

ACTION – Agent for the treatment of gastrointestinal and psychotic disorders, particularly ulcers, that acts by antagonizing σ -receptors, with a potency comparable or slightly higher than that of haloperidol (IC_{50} = 4.52 and 8.95 nM, respectively, using brain membrane preparations and [³H]-SK&F-10047 as the ligand). In contrast to haloperidol, test compound showed negligible affinity for phencyclidine (PCP) receptors (IC_{50} >10,000 nM vs. 1.268 nM for haloperidol). *In vivo*, compound was effective in inhibiting cysteamine-induced ulcers in rats and it was 50-60 times more active than the known compound igmesine (ED_{50} = 0.137 and 5.950 mg/kg i.p., respectively). In addition, the compound protected against diarrhea induced experimentally by the bacterial endotoxin *Salmonella* lipopolysaccharide, with an ED_{50} value below 100 μ g/kg p.o. It had negligible acute toxicity in rats. Within this series of 2-(arylalkenyl)azacycloalkane derivatives, the following are also included:



Compound	R1	A	Isomer	Formula
270947	cyclopropyl	-CH2-	E	C ₁₇ H ₂₃ N.HCl
270948	cyclopropyl	-CH2-	(+)-(E)	C ₁₇ H ₂₃ N.HCl
270949	cyclopropyl	-CH2-	(-)-(E)	C ₁₇ H ₂₃ N.HCl
270950	cyclopropyl-CH2	-CH2-	E	C ₁₈ H ₂₅ N.HCl
270951	CH2Ph	-CH2-	E	C ₂₁ H ₂₅ N.HCl
270952	cyclopropyl	-(CH2)2-	E	C ₁₈ H ₂₅ N.HCl
270953	cyclopropyl	-(CH2)2-	(+)-(E)	C ₁₈ H ₂₅ N.HCl
270954	cyclopropyl	-(CH2)2-	(-)-(E)	C ₁₈ H ₂₅ N.HCl
270955	cyclobutyl	-(CH2)2-	E	C ₁₉ H ₂₇ N.HCl
270956	CH2Ph	-(CH2)2-	E	C ₂₂ H ₂₇ N.HCl
270957	cyclopropyl	-(CH2)2-	Z	C ₁₈ H ₂₅ N.HCl

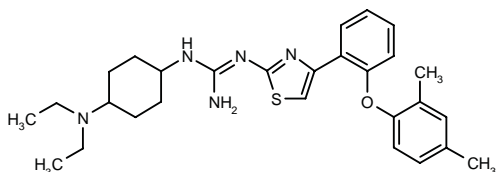
SOURCE – Jouveinal.

REFERENCES

1. Calvet, A.P. et al. (Institut de Recherche Jouveinal) *2-(Arylalkenyl)azacycloalkane derivs. as ligands for sigma receptors*. US 5849760, WO 9515948.

271462

*N*¹-[4-(Diethylamino)cyclohexyl]-*N*²-[4-[2-(2,4-dimethylphenoxy)phenyl]thiazol-2-yl]guanidine



C28 H37 N5 O S; Mol wt: 491.7003

ACTION – Antimicrobial agent with activity against *Helicobacter pylori*, representative of a series of substituted aminothiazoles.

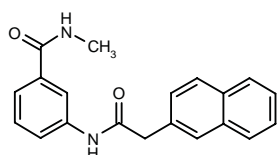
SOURCE – Bayer.

REFERENCES

1. Baasner, B. et al. (Bayer AG) *Subst. aminothiazoles and the use thereof as active antimicrobial substances*. WO 9850373.

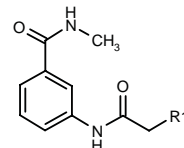
271508

N-Methyl-3-[2-(2-naphthyl)acetamido]benzamide



C20 H18 N2 O2; Mol wt: 318.3742

ACTION – Antiulcer agent with potent activity against *Helicobacter pylori* (MIC = 0.05 µg/ml against *H. pylori* strain 31A) and also found to possess inhibitory activity against *Campylobacter jejuni* (MIC = 0.008 µg/ml). LD₅₀ > 2000 mg/kg p.o. in rats. Other specifically claimed compounds from this series of amide derivatives include the following:



Compound	R1	Formula
271509	1-Naph	C ₂₀ H ₁₈ N ₂ O ₂
271510	3-benzothieryl	C ₁₈ H ₁₆ N ₂ O ₂ S
271511	4-benzothieryl	C ₁₈ H ₁₆ N ₂ O ₂ S
271512	1-Naph-O	C ₂₀ H ₁₈ N ₂ O ₃

SOURCE – Mitsubishi Chemical.

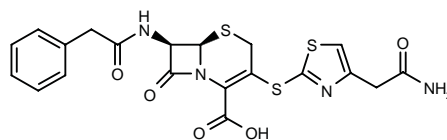
REFERENCES

1. Ando, R. et al. (Mitsubishi Chemical Corp.) *Amide derivs*. EP 887341.

FR-193879*

255013

(6*R*,7*R*)-3-[4-(Carbamoylmethyl)thiazol-2-ylsulfanyl]-7-(2-phenylacetamido)-3-cephem-4-carboxylic acid



C20 H18 N4 O5 S3; Mol wt: 490.5832

ACTION – Cephalosporin antibiotic with potent activity against *Helicobacter pylori* and Gram-positive bacteria, in particular staphylococci and streptococci. *In vitro* compound was active against clinical isolates of *H. pylori* (MIC₅₀ = 0.00078 µg/ml; MIC₉₀ = 0.00625 µg/ml) and it was also active against clarithromycin-resistant strains (MIC = 0.0016 µg/ml) and metronidazole-resistant strains. In mice infected with *H. pylori*, compound exhibited therapeutic efficacy higher than that of ampicillin and clarithromycin. Compound has strong affinity for penicillin-binding proteins (PBPs) of *H. pylori* and, like ampicillin, exhibits bactericidal activity against *H. pylori*. Moreover, it has a low potential for causing diarrhea.

SOURCE – Fujisawa.

REFERENCES

1. Yoshida, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *New cephem cpds. and pharmaceutical use thereof*. EP 882052, WO 9729111.

2. Matsumoto, Y. et al. *In vitro activity of FR193879, a novel anti-Helicobacter pylori cephalosporin*. Dig Dis Week (May 17-20, New Orleans) 1998, Abstr 1202.

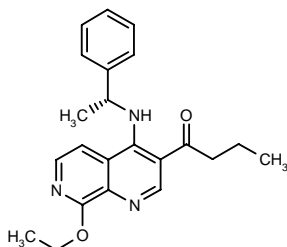
3. Yoshida, Y. et al. *Discovery of FR193879, a novel cephalosporin derivative with potent anti-Helicobacter pylori activity*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abstr 2-P-17.

*Identified compound **255013** Drug Data Report 1997, 019(11): 0999.

YJA-20379-8

270755

(+)-1-[8-Ethoxy-4-[1(*R*)-phenylethylamino]-1,7-naphthyrin-3-yl]-1-butanone



C22 H25 N3 O2; Mol wt: 363.4585

ACTION – Antiulcer agent, a reversible proton pump (H^+/K^+ -ATPase) inhibitor ($IC_{50} = 28.0 \mu M$ against enzyme from rabbit gastric mucosal membrane vesicles; IC_{50} omeprazole = $57.5 \mu M$) proven to inhibit gastric acid secretion in pylorus-ligated rats with an ED_{50} of 13.3 mg/kg intraduodenally.

SOURCE – Yung-Jin.

REFERENCES

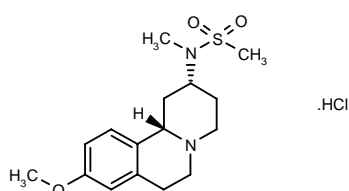
1. Yoo, H.Y. et al. (Yung-Jin Pharmaceutical Co., Ltd.) 4-Amino-3-acylnaphthyridine derivs. WO 9703074.
2. Chung, S.Y. et al. *Stability, blood partition, and pharmacokinetics of a new proton pump inhibitor, YJA-20379-8*. Res Commun Mol Pathol Pharmacol 1998, 100(2): 187.
3. Kim, H.J. et al. *Pharmacokinetic changes of a new proton pump inhibitor, YJA-20379-8, after intravenous and oral administration to rats with uranyl nitrate-induced acute renal failure*. Res Commun Mol Pathol Pharmacol 1998, 102(1): 43.
4. Kim, H.J. et al. *Pharmacokinetics of a new proton pump inhibitor, YJA-20379-8, in rats with 48-hour water deprivation*. Res Commun Mol Pathol Pharmacol 1998, 101(2): 137.

IRRITABLE BOWEL SYNDROME THERAPY

YNS-15P*

257735

(2*R*,11*bS*)-*N*-(9-Methoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-benzo[*a*]quinolizin-2-yl)-*N*-methylmethanesulfonamide hydrochloride



C16 H24 N2 O3 S . HCl; Mol wt: 360.9035

ACTION – α_2 -Adrenoceptor antagonist with a K_i value of 1.87 nM against [3H]-MK-912 binding in rat brain and about 200-fold selectivity over α_1 -adrenoceptors ($K_i = 0.369 \mu M$ for inhibition of [3H]-prazosin binding in rat brain) and no interaction with dopamine D_1 and D_2 , 5-HT $_{1A}$, 5-HT $_2$, 5-HT $_3$ and muscarinic receptors. *In vivo*, compound given both p.o. and s.c. reduced stress-stimulated fecal excretion (over 80% inhibition at 3 mg/kg s.c.) and colonic transit in rats, whereas it showed no activity on normal or bethanechol-stimulated colonic transit or fecal excretion, nor on castor oil-induced diarrhea. Potentially useful for the treatment of stress-induced colonic motor dysfunction.

SOURCE – Nippon Shinyaku.

REFERENCES

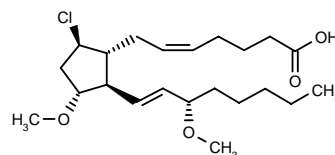
1. Yamamoto, O. and Shirouchi, Y. (Nippon Shinyaku Co., Ltd.) *Benzoquinolizine derivs. and medicinal compns*. EP 897923, WO 9740046.
2. Yamamoto, O. et al. *Effect of YNS-15P, a new α_2 adrenoceptor antagonist, on stress-stimulated colonic propulsion in rats*. J Pharmacol Exp Ther 1998, 287(2): 691.

*Identified compound 257735 Drug Data Report 1998, 020(03): 0234.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

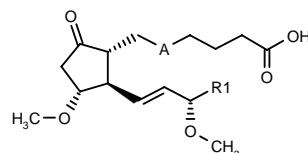
272177

9-Chloro-9-deoxy-11,15-di-*O*-methylprostaglandin F $_{2\beta}$

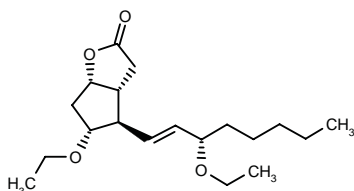


C22 H37 Cl O4; Mol wt: 400.9833

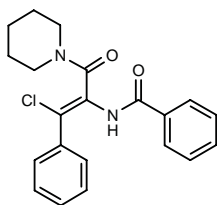
ACTION – Prostaglandin derivative with potent and selective affinity for EP $_{3\alpha}$ receptors relative to other EP receptor subtypes, as shown in a binding assay by K_i values of 0.0017, 0.039, 0.034 and 0.073 μM , respectively, for murine EP $_{3\alpha}$, EP $_1$, EP $_2$ and EP $_4$ receptors expressed in CHO cells. Potentially useful for the treatment or prevention of hepatic diseases, renal diseases, pancreatitis and myocardial infarction. Within this series of 11,15-*O*-dialkylprostaglandin E derivatives, the following are also included:



Compound	R1	A	Formula
272178	C5H11	-(Z)-CH=CH-	C ₂₂ H ₃₆ O ₅
272179	C5H11	-(CH2)2-	C ₂₂ H ₃₈ O ₅
272180	C(Me)2Bu	-(Z)-CH=CH-	C ₂₄ H ₄₀ O ₅
272181	C6H13	-(Z)-CH=CH-	C ₂₃ H ₃₈ O ₅
272182	CH2OPh	-(Z)-CH=CH-	C ₂₄ H ₃₂ O ₆

**272183:** C19 H32 O4**SOURCE** – Ono.**REFERENCES**

1. Ohuchida, S. and Maruyama, T. (Ono Pharmaceutical Co., Ltd.) *11,15-O-Dialkylprostaglandin E derivs., process for producing the same, and drugs containing the same as the active ingredient.* WO 9834916.

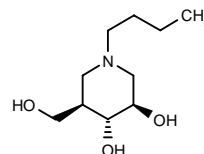
AT-61**271168****(E)-N-[2-Chloro-2-phenyl-1-(1-piperidinylcarbonyl)-ethenyl]benzamide**

C21 H21 Cl N2 O2; Mol wt: 368.8619

ACTION – Antiviral agent that selectively inhibits human hepatitis B virus replication and shows high activity against HBV in hepatoblastoma cell lines such as HepAD38 cells ($EC_{50} = 1.9 \mu M$), 2.2.15 cells ($EC_{50} = 5.7 \mu M$) and transiently transfected HepG2 cells ($EC_{50} = 2.9 \mu M$); compound did not inhibit the replication of nonhuman HBV, HIV-1, herpes simplex virus type 1 (HSV-1), vesicular stomatitis virus or Newcastle disease virus, and it had very low toxicity in a number of cell lines. It may exert its antiviral effect by interfering with the packaging of pregenomic RNA into immature core particles.

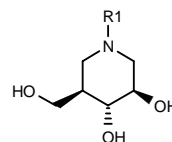
SOURCE – Triangle.**REFERENCES**

1. Perni, R.B. and Conway, S.C. (Avid Therapeutics, Inc.) *2-Benzoylamino-3-phenylpropenamide derivs. and methods of using the same.* WO 9833501.
2. King, R.W. et al. *Inhibition of human hepatitis B virus replication by AT-61, a phenylpropenamide derivative, alone and in combination with (-)-β-L-2',3'-dideoxy-3'-thiacytidine.* Antimicrob Agents Chemother 1998, 42(12): 3179.

ENDOCRINE DRUGS**ANTIDIABETIC DRUGS****271262****(3R,4R,5R)-1-Butyl-5-(hydroxymethyl)piperidine-3,4-diol**

C10 H21 N O3; Mol wt: 203.2799

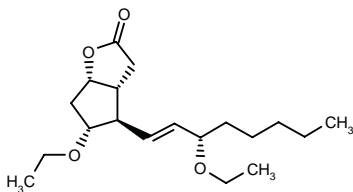
ACTION – Hypoglycemic agent that inhibits glucose production in the liver by virtue of its inhibitory activity against glycogen phosphorylase, proven to lower the glucagon-mediated increase in plasma glucose in *ob/ob* mice. Potentially useful for the treatment of non-insulin-dependent diabetes, as well as the treatment or prevention of long-term complications thereof. Within this series of specifically claimed heterocyclic compounds, the following are also included:



Compound	R1	Formula
271263	cyclohexyl-(CH2)3	C ₁₅ H ₂₉ NO ₃
271264	C12H25	C ₁₈ H ₃₇ NO ₃
271265	CH2CH2OH	C ₈ H ₁₇ NO ₄
271266	4-N(Ph)2-PhCH2	C ₂₅ H ₂₅ N ₂ O ₃
271267	CH2CONH2	C ₈ H ₁₆ N ₂ O ₄
271268	CH2CO2Et	C ₁₀ H ₁₉ NO ₅
271269	4-F-PhOCH2CH2	C ₁₄ H ₂₀ FNO ₄
271270	(CH2)11CO2H	C ₁₈ H ₃₅ NO ₅
271272	6-deoxy-1-O-Me- -α-D-glucopyranos-6-yl	C ₁₃ H ₂₅ NO ₈

SOURCE – Novo Nordisk.**REFERENCES**

1. Kristiansen, M. et al. (Novo Nordisk A/S) *Novel heterocyclic cpds.* WO 9850359.



272183: C19 H32 O4

SOURCE – Ono.

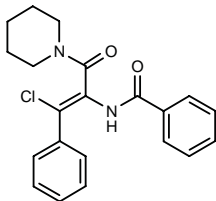
REFERENCES

1. Ohuchida, S. and Maruyama, T. (Ono Pharmaceutical Co., Ltd.) *11,15-O-Dialkylprostaglandin E derivs., process for producing the same, and drugs containing the same as the active ingredient.* WO 9834916.

AT-61

271168

(*E*)-*N*-[2-Chloro-2-phenyl-1-(1-piperidinylcarbonyl)-ethenyl]benzamide



C21 H21 Cl N2 O2; Mol wt: 368.8619

ACTION – Antiviral agent that selectively inhibits human hepatitis B virus replication and shows high activity against HBV in hepatoblastoma cell lines such as HepAD38 cells (EC₅₀ = 1.9 μM), 2.2.15 cells (EC₅₀ = 5.7 μM) and transiently transfected HepG2 cells (EC₅₀ = 2.9 μM); compound did not inhibit the replication of nonhuman HBV, HIV-1, herpes simplex virus type 1 (HSV-1), vesicular stomatitis virus or Newcastle disease virus, and it had very low toxicity in a number of cell lines. It may exert its antiviral effect by interfering with the packaging of pregenomic RNA into immature core particles.

SOURCE – Triangle.

REFERENCES

1. Perni, R.B. and Conway, S.C. (Avid Therapeutics, Inc.) *2-Benzoylamino-3-phenylpropenamide derivs. and methods of using the same.* WO 9833501.

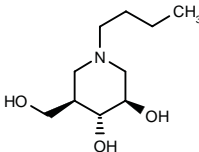
2. King, R.W. et al. *Inhibition of human hepatitis B virus replication by AT-61, a phenylpropenamide derivative, alone and in combination with (–)-β-L-2',3'-dideoxy-3'-thiacytidine.* Antimicrob Agents Chemother 1998, 42(12): 3179.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

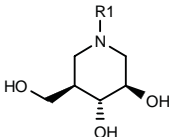
271262

(3*R*,4*R*,5*R*)-1-Butyl-5-(hydroxymethyl)piperidine-3,4-diol



C10 H21 N O3; Mol wt: 203.2799

ACTION – Hypoglycemic agent that inhibits glucose production in the liver by virtue of its inhibitory activity against glycogen phosphorylase, proven to lower the glucagon-mediated increase in plasma glucose in *ob/ob* mice. Potentially useful for the treatment of non-insulin-dependent diabetes, as well as the treatment or prevention of long-term complications thereof. Within this series of specifically claimed heterocyclic compounds, the following are also included:



Compound	R1	Formula
271263	cyclohexyl-(CH2)3	C ₁₅ H ₂₉ NO ₃
271264	C12H25	C ₁₈ H ₃₇ NO ₃
271265	CH2CH2OH	C ₈ H ₁₇ NO ₄
271266	4-N(Ph)2-PhCH2	C ₂₅ H ₂₈ N ₂ O ₃
271267	CH2CONH2	C ₈ H ₁₆ N ₂ O ₄
271268	CH2CO2Et	C ₁₀ H ₁₉ NO ₅
271269	4-F-PhOCH2CH2	C ₁₄ H ₂₀ FNO ₄
271270	(CH2)11CO2H	C ₁₈ H ₃₅ NO ₅
271272	6-deoxy-1-O-Me- -α-D-glucopyranos-6-yl	C ₁₃ H ₂₅ NO ₈

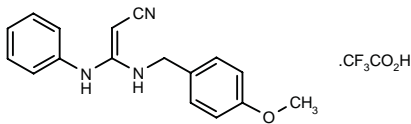
SOURCE – Novo Nordisk.

REFERENCES

1. Kristiansen, M. et al. (Novo Nordisk A/S) *Novel heterocyclic cpds.* WO 9850359.

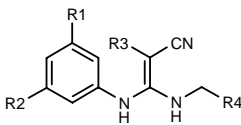
271301

3-(4-Methoxybenzylamino)-3-(phenylamino)-2-propenenitrile trifluoroacetate



C17 H17 N3 O . C2 H F3 O2; Mol wt: 393.3632

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of substituted 3,3-diamino-2-propenenitriles, the following are also included:



Compound	R1=R2	R3	R4	Formula
271302	H	CN	i-Bu	C ₁₅ H ₁₈ N ₄
271303	CF3	t-BuOCO	i-Bu	C ₂₁ H ₂₅ F ₆ N ₃ O ₂
271304	CF3	H	i-Bu	C ₁₆ H ₁₇ F ₆ N ₃
271305	CF3	CN	i-Bu	C ₁₇ H ₁₆ F ₆ N ₄
271306	CF3	4-Cl-Ph-SO ₂	i-Bu	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂ S
271307	CF3	t-BuOCO	2-oxo-perhydro- -1-azepinyl-CH ₂ CH ₂	C ₂₅ H ₃₀ F ₆ N ₄ O ₃
271308	CF3	H	2-oxo-perhydro- -1-azepinyl-CH ₂ CH ₂	C ₂₀ H ₂₂ F ₆ N ₄ O
271309	H	t-BuOCO	4-MeO-Ph	C ₂₂ H ₂₅ N ₃ O ₃

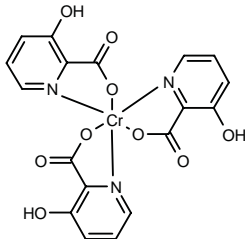
SOURCE – Novo Nordisk.

REFERENCES

1. Dörwald, F.Z. and Hansen, J.B. (Novo Nordisk A/S) *Subst. 3,3-diamino-2-propenenitriles, their preparation and use.* WO 9850344.

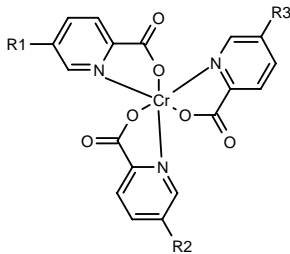
271466

Tris[3-Hydroxypyridine-2-carboxylato(1-)-κN,κO]-chromium

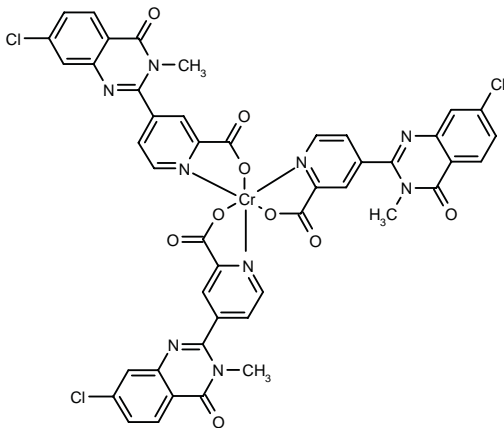


C18 H12 Cr N3 O9; Mol wt: 466.3008

ACTION – Antidiabetic agent proven to decrease plasma insulin and glucose levels (25 and 5%, respectively) in dexamethasone-treated rats at a dose of 10 mg/kg p.o. Other compounds within this series of chromium complexes include the following:



Compound	R1=R2=R3	Formula
271469	CO ₂ Et	C ₂₇ H ₂₄ CrN ₃ O ₁₂
271472	7-Cl-3-Me-4-oxo- -3,4-dihydro-2-quinazolinyl	C ₄₅ H ₂₇ Cl ₃ CrN ₉ O ₉
271473	Bu	C ₃₀ H ₃₆ CrN ₃ O ₆



271470: C45 H27 Cl3 Cr N9 O9

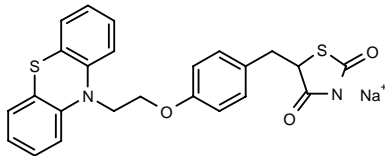
SOURCE – Otsuka.

REFERENCES

1. Kuroki, Y. (Otsuka Pharmaceutical Co., Ltd.) *Chromium complex.* JP 98298189.

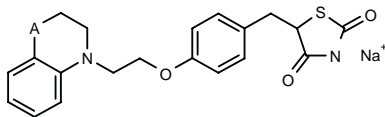
271641

5-[4-[2-(10*H*-Phenothiazin-10-yl)ethoxy]benzyl]thiazolidine-2,4-dione sodium salt



C24 H19 N2 Na O3 S2; Mol wt: 470.5471

ACTION – Hypoglycemic and hypolipidemic agent proven to produce a 43% reduction in blood glucose and a 23% reduction in triglyceride levels in *db/db* mice at a dose of 10 mg/kg p.o. Other representative compounds within this series of specifically claimed azolidinediones include the following:



Compound	A	Formula
271642	O	C ₂₀ H ₁₉ N ₂ NaO ₄ S
271643	S	C ₂₀ H ₁₉ N ₂ NaO ₃ S ₂

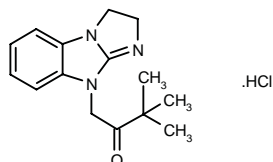
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

REFERENCES

1. Lohray, B.B. et al. (Dr. Reddy's Research Foundation) *Azolidinediones useful for the treatment of diabetes, dyslipidemia and hypertension*. WO 9852946.

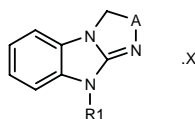
271797

1-(3,9-Dihydro-2*H*-imidazo[1,2-*a*]benzimidazol-9-yl)-3,3-dimethyl-2-butanone hydrochloride

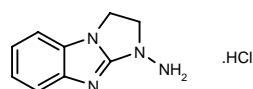


C₁₅H₁₉N₃O . HCl; Mol wt: 293.7960

ACTION – Antidiabetic agent with comparable hypoglycemic activity to gliclazide and devoid of the hepatotoxicity of structurally similar compounds. Within this series of benzimidazole tricyclic derivatives, the following are also specifically claimed:



Compound	R1	A	X	Formula
271798	1-adamantyl-COCH ₂	-CH ₂ -	HBr	C ₂₁ H ₂₅ N ₃ O.HBr
271799	t-BuCOCH ₂	-(CH ₂) ₂ -	HCl	C ₁₆ H ₂₁ N ₃ O.HCl
271800	1-adamantyl-COCH ₂	-(CH ₂) ₂ -	HBr	C ₂₂ H ₂₇ N ₃ O.HBr
271802	NH ₂	-(CH ₂) ₂ -	HCl	C ₁₀ H ₁₂ N ₄ .HCl



271801: C₉H₁₀N₄ . HCl

SOURCE – ADIR.

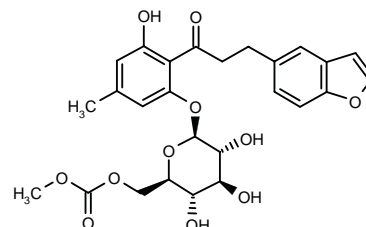
REFERENCES

1. Anisimova, V.A. et al. (ADIR et Cie.) *Novel benzimidazol tricyclic derivs., their preparation method and pharmaceutical compsns. containing them*. WO 9900390.

T-1095¹⁻⁵

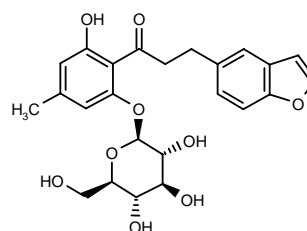
264177

3-(5-Benzofuranyl)-1-[2-hydroxy-6-[6-*O*-(methoxycarbonyl)-β-D-glucopyranosyloxy]-4-methylphenyl]-1-propanone



C₂₆H₂₈O₁₁; Mol wt: 516.4962

ACTION – Oral antidiabetic agent, a prodrug of the potent and selective inhibitor of the sodium-glucose cotransporter (SGLT) **T-0115**. Compound inhibited α-methylglucopyranoside uptake in *Xenopus* oocytes expressing human SGLT1 and SGLT2, with *K_i* values of 9.8 and 0.9 μM, respectively. In rats T-1095 given at oral doses of 30-100 mg/kg increased urinary glucose excretion. In mice, compound suppressed elevated blood glucose levels and increased the urinary excretion of glucose following both oral and s.c. glucose loads, indicating that inhibition of renal glucose reabsorption may contribute to its hypoglycemic effect. In two models of experimental diabetes in rats, orally administered compound markedly decreased blood glucose and normalized impaired insulin sensitivity.



T-0115^{1,2} [268360]: C₂₄H₂₆O₉

SOURCE – Tanabe.

REFERENCES

1. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Propiophenone derivs. and process for preparing the same*. EP 850948, JP 98237089.

2. Kawanishi, H. et al. *Na⁺-glucose cotransporter inhibitors as antidiabetic agents (2)*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-27.

3. Nawano, M. et al. *Improvement of insulin secretion and insulin sensitivity in ZDF rats associated with reduction in blood glucose levels by T-1095, a SGLT inhibitor*. J Jpn Diabetes Soc 1998, 41(Suppl. 1): Abst 2F 17.

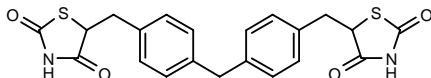
4. Nawano, M. et al. *T-1095, a novel specific inhibitor of SGLT, is a promising drug for diabetes treatment*. Diabetes 1998, 47(Suppl. 1): Abst 1379.

5. Oku, A. et al. *Improvement of hyperglycemia by a novel orally active inhibitor of Na-glucose cotransporter*. Diabetes 1998, 47(Suppl. 1): Abst 1606.

YM-268

262300

5,5'-Methylenebis(1,4-phenylene)bismethylenebis-(thiazolidine-2,4-dione)



C₂₁ H₁₈ N₂ O₄ S₂; Mol wt: 426.5152

ACTION – Potent thiazolidinedione insulin sensitizer that appears to increase glucose uptake, at least in part, by enhancing the expression of the glucose transporters GLUT1 and GLUT4 via activation of peroxisome proliferator-activated receptor γ (PPAR γ). In obese Zucker rats, it improved hyperglycemia, hyperinsulinemia and impaired glucose tolerance at a dose of 10 mg/kg p.o. for 14 days. Potentially useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Yamanouchi.

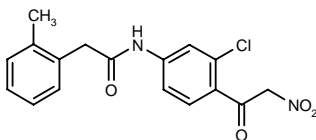
REFERENCES

1. Niigata, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Bisheterocyclic cpd.* JP 92511153, WO 9200967.
2. Shimaya, A. et al. *Insulin sensitizer YM268 ameliorates insulin resistance by normalizing the decreased content of GLUT4 in adipose tissue of obese Zucker rats.* Eur J Endocrinol 1997, 137(6): 693.
3. Shimaya, A. et al. *YM268 increases the glucose uptake, cell differentiation, and mRNA expression of glucose transporter in 3T3-L1 adipocytes.* Horm Metab Res 1998, 30(9): 543.

TREATMENT OF DIABETIC COMPLICATIONS

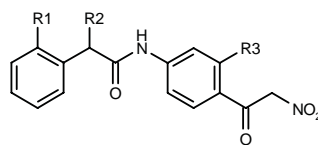
271323

N-[3-Chloro-4-(2-nitroacetyl)phenyl]-2-(2-methylphenyl)-acetamide

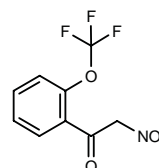


C₁₇ H₁₅ Cl N₂ O₄; Mol wt: 346.7685

ACTION – A potent aldose reductase inhibitor (IC₅₀ = 7 nM against enzyme from rat crystalline lens) found to produce 70% inhibition of sorbitol accumulation in sciatic nerve in streptozotocin-diabetic rats at 10 mg/kg p.o. given at 4, 30 and 52 h after streptozotocin injection. Potentially useful for the treatment or prevention of diabetic complications. A representative compound from a series of nitromethyl ketones, wherein the following are also included:



Compound	R1	R2	R3	Formula
271325	H	Me	Cl	C ₁₇ H ₁₅ ClN ₂ O ₄
271326	H	H	Cl	C ₁₆ H ₁₃ ClN ₂ O ₄
271327	H	Cl	Cl	C ₁₆ H ₁₂ Cl ₂ N ₂ O ₄
271328	CF ₃	H	Cl	C ₁₇ H ₁₂ ClF ₃ N ₂ O ₄
271329	Me	H	Me	C ₁₈ H ₁₈ N ₂ O ₄



271324: C₉ H₆ F₃ N O₄

SOURCE – Merck KGaA.

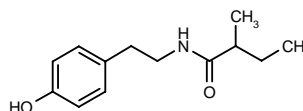
REFERENCES

1. Lardy, C. et al. (Merck Patent GmbH) *New nitromethyl ketones, process for preparing them and compsns. containing them.* WO 9852906.

YUA-001

269609

N-[2-(4-Hydroxyphenyl)ethyl]-3-methylbutanamide



C₁₃ H₁₉ N O₂; Mol wt: 221.2981

White powder, m.p. 103 °C.

ACTION – Aldose reductase inhibitor isolated from the fermentation broth of alkalophilic *Corynebacterium* sp. YUA25, found to interact noncompetitively with pig kidney aldose reductase, with a potency (IC₅₀ = 1.8 mM) 2 orders of magnitude less than tolrestat (IC₅₀ = 16 μ M). Compound has no antimicrobial activity against Gram-positive or Gram-negative bacteria, fungi or yeast. Modifications to the compound are being pursued with the aim of discovering compounds for the treatment of diabetic complications such as cataracts, retinopathy, neuropathy and nephropathy.

SOURCE – Fujisawa.

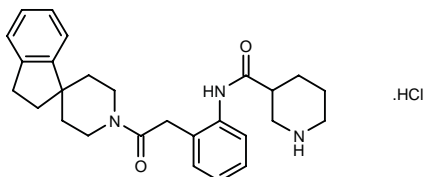
REFERENCES

1. Bahn, Y.-S. et al. *YUA001, a novel aldose reductase inhibitor isolated from alkalophilic Corynebacterium sp. YUA25. I. Taxonomy, fermentation, isolation and characterization.* J Antibiot 1998, 51(10): 902.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

270469

N-[2-[2-Oxo-2-(spiro[2,3-dihydroindene-1,4'-piperidin]-1'-yl)ethyl]phenyl]piperidine-3-carboxamide hydrochloride



C₂₇ H₃₃ N₃ O₂ . HCl; Mol wt: 468.0376

ACTION – Growth hormone (GH) secretagogue whose stimulant activity was evaluated *in vitro* in isolated rat pituitary cells (EC₅₀ = 34 nM). A representative compound within a series of benzene derivatives.

SOURCE – Sumitomo Pharmaceuticals.

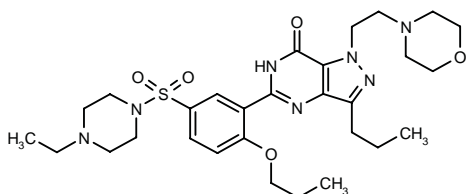
REFERENCES

1. Ueki, Y. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Benzene derivs.* WO 9846569.

TREATMENT OF MALE SEXUAL DYSFUNCTION

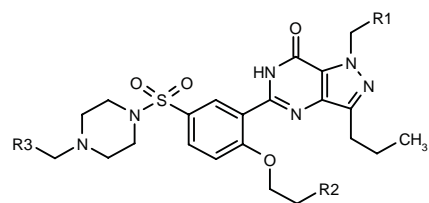
271135

5-[5-(4-Ethyl-1-piperazinylsulfonyl)-2-propoxyphenyl]-1-[2-(4-morpholinyl)ethyl]-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

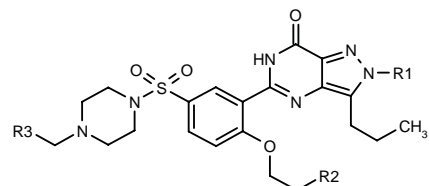


C₂₉ H₄₃ N₇ O₅ S; Mol wt: 601.7687

ACTION – Agent for the treatment of male erectile dysfunction and female sexual dysfunction, an inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 1.9 nM). Other representative compounds within this series of pyrazolopyrimidinones include the following:



Compound	R1	R2	R3	Formula
271138	2-Pyr	Me	CH ₂ OH	C ₂₉ H ₃₇ N ₇ O ₅ S
271140	1-Me-1,2,4-triazol-5-yl-CH ₂	Me	H	C ₂₈ H ₃₆ N ₉ O ₄ S
271143	Ph	H	H	C ₂₈ H ₃₄ N ₆ O ₄ S



Compound	R1	R2	R3	Formula
271139	2-Pyr-CH ₂	Me	CH ₂ OH	C ₂₉ H ₃₇ N ₇ O ₅ S
271141	1-Me-1,2,4-triazol-5-yl-CH ₂	Me	H	C ₂₈ H ₃₆ N ₉ O ₄ S
271144	CH ₂ Ph	H	H	C ₂₈ H ₃₄ N ₆ O ₄ S
271146	4-morpholinyl-CH ₂ CH ₂	Me	Me	C ₂₉ H ₄₃ N ₇ O ₅ S
271147	2-(MeSO ₂ NH)-Ph	Me	Me	C ₃₀ H ₃₈ N ₇ O ₆ S ₂
271148	2-pyrimidinyl	Me	H	C ₂₈ H ₃₂ N ₈ O ₄ S
271149	cyclobutyl-CH ₂	H	H	C ₂₈ H ₃₆ N ₆ O ₄ S
271150	1-oxido-2-Pyr-CH ₂	Me	Me	C ₂₉ H ₃₇ N ₇ O ₅ S

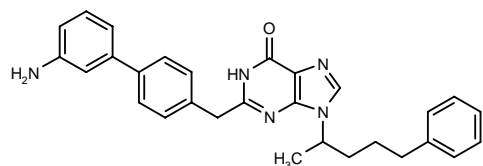
SOURCE – Pfizer.

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1. Bunnage, M.E. et al. (Pfizer Ltd.;Pfizer Inc.) *Pyrazolopyrimidinones which inhibit type 5 cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE5) for the treatment of sexual dysfunction.* WO 9849166.

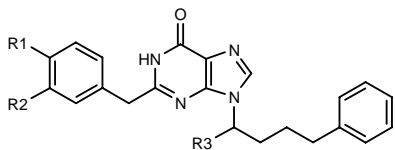
271724

2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenyl-butyl)hypoxanthine



C₂₉ H₂₉ N₅ O; Mol wt: 463.5821

ACTION – An inhibitor of phosphodiesterases (PDE) including PDE1 (IC₅₀ = 100 nM), PDE2 (IC₅₀ = 20 nM) and PDE5 (IC₅₀ = 500 nM), claimed for use in the treatment of impotence, incontinence and prostatic hypertrophy and also potentially useful in the treatment of a range of cardiovascular and cerebrovascular disorders. Other representative compounds within this series of purin-6-one derivatives include the following:



Compound	R1	R2	R3	Formula
271725	H	H	Me	C ₂₃ H ₂₄ N ₄ O
271726	Cl	Cl	CH(OH)Me	C ₂₄ H ₂₄ Cl ₂ N ₄ O ₂
271727	F	H	Me	C ₂₃ H ₂₃ FN ₄ O
271728	3-thienyl	H	Me	C ₂₇ H ₂₆ N ₄ OS
271729	OMe	4-CO ₂ H-1-Pip-SO ₂	CH(OH)Me	C ₃₁ H ₃₇ N ₅ O ₇ S

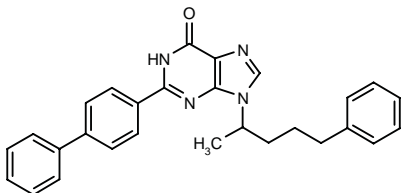
SOURCE – Bayer.

REFERENCES

1. Niewöhner, U. et al. (Bayer AG) *Purin-6-one derivs.* US 5861396.

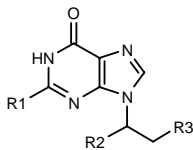
271779

2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1*H*-purin-6-one



C₂₈ H₂₆ N₄ O; Mol wt: 434.5404

ACTION – Agent for the treatment of impotence, as well as thromboembolic, cardiovascular and inflammatory disorders, that acts by inhibiting phosphodiesterase types 1, 2 and 5 (PDE1, PDE2 and PDE5), with IC₅₀ values of 1, 0.4 and 1 μM, respectively. Other compounds within this series of 2,9-disubstituted purin-6-ones include the following:



Compound	R1	R2	R3	Formula
271780	4-Cl-Ph	CH(OH)Me	C ₅ H ₁₁	C ₂₀ H ₂₅ ClN ₄ O ₂
271781	cyclohexyl	CH(OH)Me	CH ₂ CH ₂ Ph	C ₂₃ H ₃₀ N ₄ O ₂
271782	cyclopropyl	(CH ₂) ₃ Ph	H	C ₁₉ H ₂₂ N ₄ O
271783	1,3-benzodioxol-5-yl	(CH ₂) ₃ Ph	H	C ₂₃ H ₂₂ N ₄ O ₃

SOURCE – Bayer.

REFERENCES

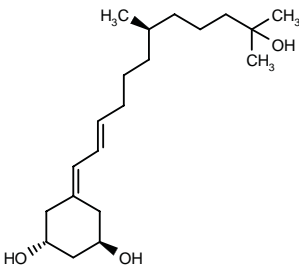
1. Niewöhner, U. et al. (Bayer AG) *2,9-Disubstd. purin-6-ones.* US 5861404.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

271322

(1*R*,3*R*)-5-[11-Hydroxy-7(*R*),11-dimethyldodec-2(*E*)-enylidene]cyclohexane-1,3-diol



C₂₀ H₃₆ O₃; Mol wt: 324.5014

ACTION – Agent for the treatment or prevention of hyperproliferative skin diseases, particularly psoriasis, basal cell carcinomas, disorders of keratinization and keratosis, as well as for reversing conditions associated with photodamage. When tested in minipigs, compound was found to increase epidermal proliferation at 100-4000 μg/kg p.o. and was extremely well tolerated.

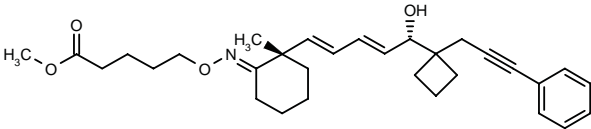
SOURCE – Roche.

REFERENCES

1. Bauer, F. and Courtney, L.F. (F. Hoffmann-La Roche AG) *Cyclohexanediol derivs.* WO 9852894.

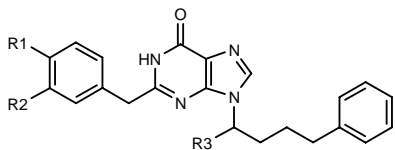
271357

5-[2(*S*)-[5(*S*)-Hydroxy-5-[1-(3-phenyl-2-propynyl)-cyclobutyl]-1(*E*),3(*E*)-pentadienyl]-2-methyl-1(*E*)-cyclohexylideneaminoxy]pentanoic acid methyl ester



C₃₁ H₄₁ N O₄; Mol wt: 491.6679

ACTION – Antiinflammatory, antiallergic and antiproliferative agent with LTB₄ (BLT)-antagonist activity, reported to be particularly useful in the treatment of psoriasis, atopic dermatitis and other dermatological proliferative disorders, as well as asthma, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and the like. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
271725	H	H	Me	C ₂₃ H ₂₄ N ₄ O
271726	Cl	Cl	CH(OH)Me	C ₂₄ H ₂₄ Cl ₂ N ₄ O ₂
271727	F	H	Me	C ₂₃ H ₂₃ FN ₄ O
271728	3-thienyl	H	Me	C ₂₇ H ₂₆ N ₄ OS
271729	OMe	4-CO ₂ H-1-Pip-SO ₂	CH(OH)Me	C ₃₁ H ₃₇ N ₅ O ₇ S

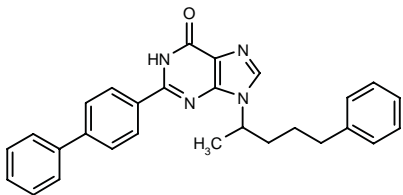
SOURCE – Bayer.

REFERENCES

1. Niewöhner, U. et al. (Bayer AG) *Purin-6-one derivs.* US 5861396.

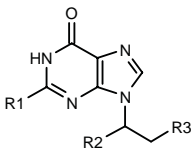
271779

2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1*H*-purin-6-one



C₂₈ H₂₆ N₄ O; Mol wt: 434.5404

ACTION – Agent for the treatment of impotence, as well as thromboembolic, cardiovascular and inflammatory disorders, that acts by inhibiting phosphodiesterase types 1, 2 and 5 (PDE1, PDE2 and PDE5), with IC₅₀ values of 1, 0.4 and 1 μM, respectively. Other compounds within this series of 2,9-disubstituted purin-6-ones include the following:



Compound	R1	R2	R3	Formula
271780	4-Cl-Ph	CH(OH)Me	C ₅ H ₁₁	C ₂₀ H ₂₅ ClN ₄ O ₂
271781	cyclohexyl	CH(OH)Me	CH ₂ CH ₂ Ph	C ₂₃ H ₃₀ N ₄ O ₂
271782	cyclopropyl	(CH ₂) ₃ Ph	H	C ₁₉ H ₂₂ N ₄ O
271783	1,3-benzodioxol-5-yl	(CH ₂) ₃ Ph	H	C ₂₃ H ₂₂ N ₄ O ₃

SOURCE – Bayer.

REFERENCES

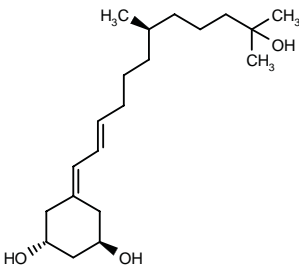
1. Niewöhner, U. et al. (Bayer AG) *2,9-Disubstd. purin-6-ones.* US 5861404.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

271322

(1*R*,3*R*)-5-[11-Hydroxy-7(*R*),11-dimethyldodec-2(*E*)-enylidene]cyclohexane-1,3-diol



C₂₀ H₃₆ O₃; Mol wt: 324.5014

ACTION – Agent for the treatment or prevention of hyperproliferative skin diseases, particularly psoriasis, basal cell carcinomas, disorders of keratinization and keratosis, as well as for reversing conditions associated with photodamage. When tested in minipigs, compound was found to increase epidermal proliferation at 100-4000 μg/kg p.o. and was extremely well tolerated.

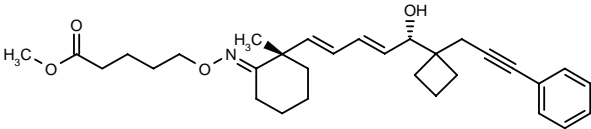
SOURCE – Roche.

REFERENCES

1. Bauer, F. and Courtney, L.F. (F. Hoffmann-La Roche AG) *Cyclohexanediol derivs.* WO 9852894.

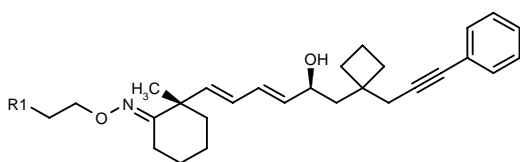
271357

5-[2(*S*)-[5(*S*)-Hydroxy-5-[1-(3-phenyl-2-propynyl)-cyclobutyl]-1(*E*),3(*E*)-pentadienyl]-2-methyl-1(*E*)-cyclohexylideneaminoxy]pentanoic acid methyl ester

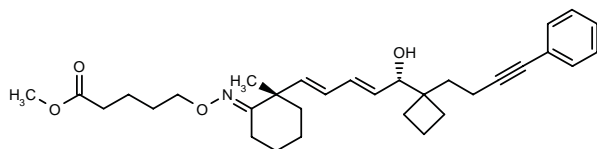


C₃₁ H₄₁ N O₄; Mol wt: 491.6679

ACTION – Antiinflammatory, antiallergic and antiproliferative agent with LTB₄ (BLT)-antagonist activity, reported to be particularly useful in the treatment of psoriasis, atopic dermatitis and other dermatological proliferative disorders, as well as asthma, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and the like. Other exemplified compounds include the following:



Compound	R1	Formula
271358	CH ₂ CH ₂ CO ₂ Me	C ₃₂ H ₄₃ NO ₄
271360	(CH ₂) ₃ CO ₂ Et	C ₃₄ H ₄₇ NO ₄
271361	C(Me) ₂ CH ₂ CO ₂ Me	C ₃₄ H ₄₇ NO ₄



271359: C₃₂ H₄₃ N O₄

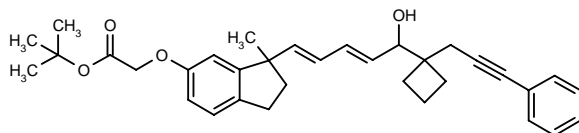
SOURCE – Schering AG.

REFERENCES

1. Buchmann, B. et al. (Schering AG) *Leukotriene B₄ derivs., in particular oximo-LTB₄ antagonists*. WO 9852915.

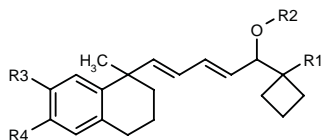
271362

(±)-2-[3-[5-Hydroxy-5-[1-(3-phenyl-2-propynyl)cyclobutyl]-1(*E*),3(*E*)-pentadienyl]-3-methyl-2,3-dihydro-1*H*-inden-5-yloxy]acetic acid *tert*-butyl ester

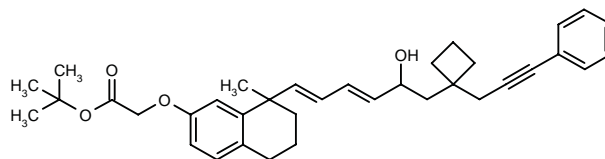


C₃₄ H₄₀ O₄; Mol wt: 512.6860

ACTION – Antiinflammatory, antiallergic and antiproliferative agent, an LTB₄ (BLT) antagonist reported to be particularly useful in the treatment of psoriasis, atopic dermatitis and other dermatological proliferative disorders, as well as asthma, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and the like. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
271363	CH ₂ -ethynylene-Ph	H	H	<i>t</i> -BuO-COCH ₂ O	C ₃₅ H ₄₂ O ₄
271364	CH ₂ -ethynylene-Ph	Ac	<i>t</i> -BuO-COCH ₂ O	H	C ₃₇ H ₄₂ O ₅
271365	4-Ph-Ph	H	<i>t</i> -BuO-COCH ₂ O	H	C ₃₈ H ₄₄ O ₄
271366	CH ₂ CH ₂ -ethynylene-Ph	H	<i>t</i> -BuO-COCH ₂ O	H	C ₃₆ H ₄₄ O ₄



271367: C₃₆ H₄₄ O₄

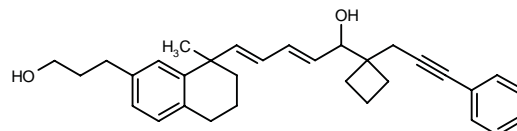
SOURCE – Schering AG.

REFERENCES

1. Buchmann, B. et al. (Schering AG) *Leukotriene B₄ antagonists, in particular 3-oxatetrahydronaphthalene-LTB₄ antagonists*. WO 9852913.

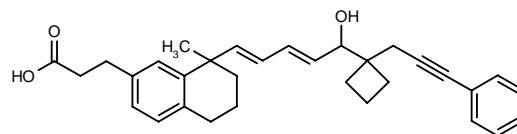
271368

5-[7-(3-Hydroxypropyl)-1-methyl-1,2,3,4-tetrahydro-1-naphthalenyl]-1-[1-(3-phenyl-2-propynyl)cyclobutyl]-2(*E*),4(*E*)-pentadien-1-ol



C₃₂ H₃₈ O₂; Mol wt: 454.6502

ACTION – Antiinflammatory, antiallergic and antiproliferative agent with LTB₄ (BLT)-antagonist activity, reported to be particularly useful in the treatment of psoriasis, atopic dermatitis and other dermatological proliferative disorders, as well as asthma, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and the like. Another exemplified compound is:



271369: C₃₂ H₃₆ O₃

SOURCE – Schering AG.

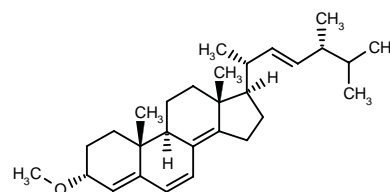
REFERENCES

1. Buchmann, B. et al. (Schering AG) *Leukotriene B₄ antagonists, in particular 3-carbatetrahydronaphthalene-LTB₄ antagonists*. WO 9852912.

MISCELLANEOUS DERMATOLOGIC DRUGS

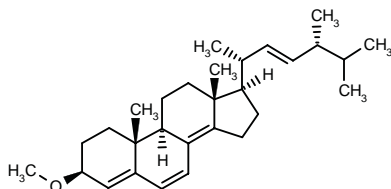
271565

3α-Methoxyergosta-4,6,8(14),22(*E*)-triene



C₂₉ H₄₄ O; Mol wt: 408.6656

ACTION – Antiallergic steroid extracted from *Elfvigia applanata* or obtained by chemical synthesis, with IL-4 and IL-2 production-inhibitory activity. Particularly useful for the treatment of atopic dermatitis. An isomer of this compound is:



271566: C29 H44 O

SOURCE – Kao.

REFERENCES

1. Kusuoku, H. et al. (Kao Corporation) *Novel steroid cpds. and IL-4 production inhibitors containing the same cpds. as effective ingredient.* JP 98291997.

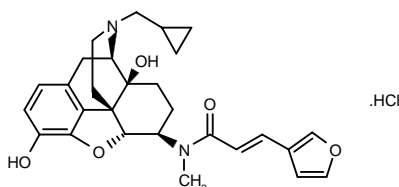
TRK-820*

217944

266168 (as free base)

N-[*N*-(Cyclopropylmethyl)-4,5(*R*)-epoxy-3,14-dihydroxymorphinan-6(*R*)-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride

[4*R*-(4 α ,4 α β ,7 β ,7 α β ,12 β S)]-*N*-[3-(Cyclopropylmethyl)-4 α ,9-dihydroxy-4,12-methano-2,3,4,4 α ,5,6,7,7 α -octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride



C28 H32 N2 O5 . HCl; Mol wt: 513.0307

ACTION – Potent and selective, nonpeptide κ -opioid receptor agonist with potency 4000-fold higher than that of morphine in both guinea pig ileum and mouse vas deferens (IC_{50} = 4.8 and 36 pM, respectively). The selectivity of the compound for κ - over μ -receptors was 279 in guinea pig ileum and 104 in mouse vas deferens and the selectivity over δ -receptors was 135 in mouse vas deferens. In the mouse writhing test and rat tail-flick test, compound given s.c. exhibited antinociceptive activity, with ED_{50} values of 3.3 and 62 μ g/kg, respectively, being 85-140 times more potent than morphine. Compound is devoid of aversive effect and did not induce dependence in the conditioned place-preference test. Clinical studies with TRK-820 had reached phase II in Japan and phase I in the U.S., but emphasis was subsequently shifted to TRK-870 as an analgesic and the development of TRK-820 was refocused to the indication of pruritus.

SOURCES – Daiichi Pharmaceutical; Toray.

REFERENCES

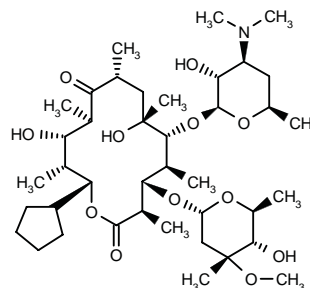
1. Nagase, H. et al. (Toray Industries, Inc.) *Antipruritic agent.* EP 897726, WO 9823290.
 2. Nagase, H. et al. (Toray Industries, Inc.) *Antitussive.* EP 657163, JP 95503397, US 5739145, WO 9501178.
 3. Nagase, H. et al. (Toray Industries, Inc.) *Morphinan deriv. and medicinal use.* EP 577847, EP 846694, JP 94509616, WO 9315081.
 4. Nagase, H. et al. (Toray Industries, Inc.) *Morphinan deriv. and medicinal use.* EP 663401, JP 95505061, WO 9503308.
 5. Nagase, H. *Rational design and synthesis of non-peptide κ opioid agonist.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst S23-5.
 6. Nagase, H. et al. *Discovery of a structurally novel opioid κ -agonist derived from 4,5-epoxymorphinan.* Chem Pharm Bull 1998, 46(2): 366.
 7. Nagase, H. et al. *Rational drug design and synthesis of opioid κ - and δ -receptor selective agonists.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst IL-11.
 8. Xiao, P. et al. *The antinociceptive effects of matrine type lupin alkaloids.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-22.
 9. *New direction taken in Toray's analgesic drug program.* Prous Science Daily Essentials 1998, May 7.
 10. *Toray analgesic in clinical development worldwide.* Prous Science Daily Essentials 1998, April 23.
 11. *Toray and Daiichi Pharmaceutical to develop powerful non-narcotic analgesic.* Toray Ind., Inc. Press Release 1997, June 23.
 12. *Toray's new analgesic agent TRK-820 to enter clinical trials (phase I) in November 1994.* Nikkei Sangyo Shinbun 1994, October 19.
 13. *Toray/Daiichi to begin clinical development of non-narcotic analgesic.* Prous Science Daily Essentials 1997, Nov 25.
 14. Daiichi Pharmaceutical Co., Ltd. Product Pipeline 1998, November.
- *Identified compound **266168** Drug Data Report 1998, 020(09): 0788.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

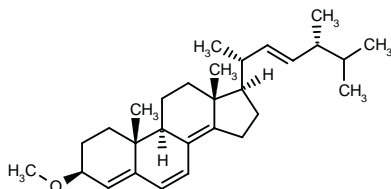
270411

13-Cyclopentyl-13-deethyl-12-deoxyerythromycin



C40 H71 N O12; Mol wt: 757.9959

ACTION – Antiallergic steroid extracted from *Elfvigia applanata* or obtained by chemical synthesis, with IL-4 and IL-2 production-inhibitory activity. Particularly useful for the treatment of atopic dermatitis. An isomer of this compound is:



271566: C29 H44 O

SOURCE – Kao.

REFERENCES

1. Kusuoku, H. et al. (Kao Corporation) *Novel steroid cpds. and IL-4 production inhibitors containing the same cpds. as effective ingredient.* JP 98291997.

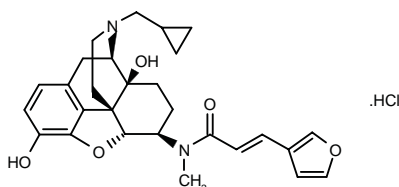
TRK-820*

217944

266168 (as free base)

N-[*N*-(Cyclopropylmethyl)-4,5(*R*)-epoxy-3,14-dihydroxymorphinan-6(*R*)-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride

[4*R*-(4 α ,4 α β ,7 β ,7 α β ,12 β S)]-*N*-[3-(Cyclopropylmethyl)-4 α ,9-dihydroxy-4,12-methano-2,3,4,4 α ,5,6,7,7 α -octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride



C28 H32 N2 O5 . HCl; Mol wt: 513.0307

ACTION – Potent and selective, nonpeptide κ -opioid receptor agonist with potency 4000-fold higher than that of morphine in both guinea pig ileum and mouse vas deferens (IC_{50} = 4.8 and 36 pM, respectively). The selectivity of the compound for κ - over μ -receptors was 279 in guinea pig ileum and 104 in mouse vas deferens and the selectivity over δ -receptors was 135 in mouse vas deferens. In the mouse writhing test and rat tail-flick test, compound given s.c. exhibited antinociceptive activity, with ED_{50} values of 3.3 and 62 μ g/kg, respectively, being 85-140 times more potent than morphine. Compound is devoid of aversive effect and did not induce dependence in the conditioned place-preference test. Clinical studies with TRK-820 had reached phase II in Japan and phase I in the U.S., but emphasis was subsequently shifted to TRK-870 as an analgesic and the development of TRK-820 was refocused to the indication of pruritus.

SOURCES – Daiichi Pharmaceutical; Toray.

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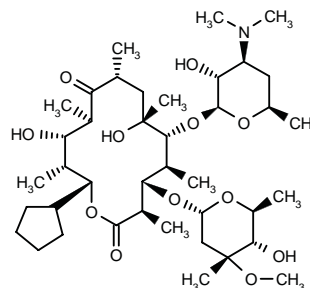
1. Nagase, H. et al. (Toray Industries, Inc.) *Antipruritic agent.* EP 897726, WO 9823290.
 2. Nagase, H. et al. (Toray Industries, Inc.) *Antitussive.* EP 657163, JP 95503397, US 5739145, WO 9501178.
 3. Nagase, H. et al. (Toray Industries, Inc.) *Morphinan deriv. and medicinal use.* EP 577847, EP 846694, JP 94509616, WO 9315081.
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 6. Nagase, H. et al. *Discovery of a structurally novel opioid κ -agonist derived from 4,5-epoxymorphinan.* Chem Pharm Bull 1998, 46(2): 366.
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 13. *Toray/Daiichi to begin clinical development of non-narcotic analgesic.* Prous Science Daily Essentials 1997, Nov 25.
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- *Identified compound **266168** Drug Data Report 1998, 020(09): 0788.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

270411

13-Cyclopentyl-13-deethyl-12-deoxyerythromycin



C40 H71 N O12; Mol wt: 757.9959

ACTION – C-13 substituted erythromycin produced by a recombinant *Saccharopolyspora erythraea* strain fed exogenous short-chain fatty acids. Compound showed good activity against *Pasteurella multocida*, *Escherichia coli* and *Staphylococcus aureus* (MIC = 0.025, 0.1 and 1.56 µg/ml, respectively), being more active against *E. coli* and *P. multocida* than erythromycin A and B.

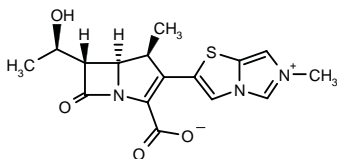
SOURCE – Pfizer.

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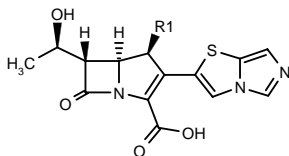
270474

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-(6-methylimidazo[5,1-*b*]thiazolium-2-yl)-1-carba-2-penam-3-carboxylate



C16 H17 N3 O4 S; Mol wt: 347.3933

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* M126 (MIC = 3.13 µg/ml), penicillin-resistant *Streptococcus pneumoniae* PRC9 (MIC = 0.05 µg/ml), *Haemophilus influenzae* PRC2 (MIC = 0.05 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC < 0.025 µg/ml) and β-lactamase-producing strains. It is stable to hydrolysis by renal dehydropeptidase (DHP-I). Other representative compounds within this series of carbapenem derivatives include the following:



Compound	R1	Formula
270475	Me	C ₁₅ H ₁₅ N ₃ O ₄ S
270476	H	C ₁₄ H ₁₃ N ₃ O ₄ S

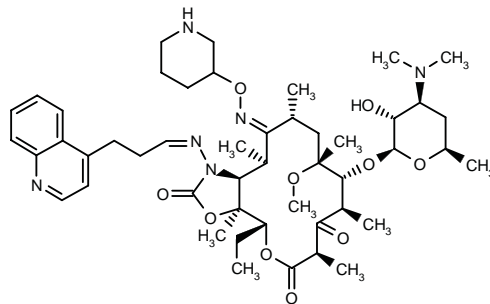
SOURCE – Meiji Seika.

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- Kano, Y. et al. (Meiji Seika Kaisha, Ltd.) *New carbapenem derivs*. WO 9832760.

270910

9-Deoxo-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-9(*E*)-(piperidin-3-yloxyimino)-11-[3-(quinolin-4-yl)propylidenehydrazino]erythromycin A *N*¹¹,*O*¹²-cyclic carbamate



C48 H72 N6 O10; Mol wt: 893.1288

ACTION – Antibacterial erythromycin derivative with potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.3 µg/ml), *Streptococcus pyogenes* group A 02A1UC1 (MIC = 0.08 µg/ml), *Streptococcus agalactiae* group B 02B1HT1 (MIC = 0.08 µg/ml), *Streptococcus faecalis* group D 02D2UC1 (MIC = 0.08 µg/ml), *Streptococcus faecium* group D 02D3HT1 (MIC = 0.08 µg/ml) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.02 µg/ml or less).

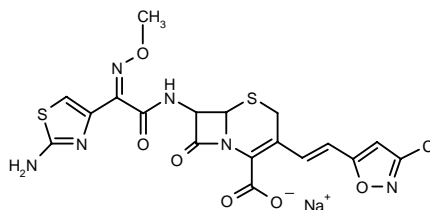
SOURCE – Hoechst Marion Roussel.

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- Agouridas, C. et al. (Hoechst Marion Roussel, SA) *Novel erythromycin derivs., method of preparation and application as medicines*. WO 9838199.

271166

7-[2-(2-Aminothiazolyl-4-yl)-2(*Z*)-(methoxyimino)-acetamido]-3-(3-chloroisoxazol-5-ylvinyl)-3-cephem-4-carboxylic acid sodium salt



C18 H14 Cl N6 Na O6 S2; Mol wt: 532.9196

ACTION – Cephalosporin antibiotic active against Gram-positive bacteria such as *Staphylococcus aureus* (MIC = 0.195-0.781 µg/ml) and *Streptococcus pyogenes* (MIC = 0.004 µg/ml), as well as against certain Gram-negative microorganisms such as *Escherichia coli* (MIC = 0.098 µg/ml), *Salmonella typhimurium* (MIC = 0.098 µg/ml) and *Enterobacter cloacae* (MIC = 0.049 µg/ml). Based on its antibacterial activity and good pharmacokinetic profile in mice after both oral and s.c. administration, compound was selected as a promising candidate for optimization as a parenteral and oral antibiotic.

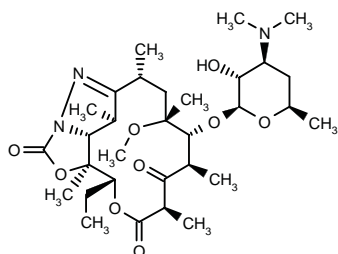
SOURCE – Korea Institute of Science and Technology, Seoul, (KR).

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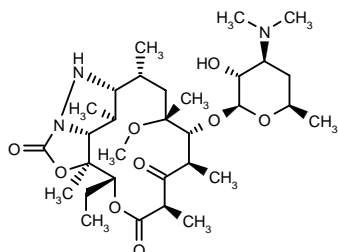
271377

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-11-methoxy-3a,7,9,11,13,15-hexamethyl-10-[3,4,6-trideoxy-3-(dimethylamino)- β -D-glucopyranosyloxy]-3a,4,6,7,8,9,10,11,12,13,15,15a-dodecahydro-2*H*-1,4-nitrilooxacyclotetradecino[4,3-*d*]oxazol-2-one

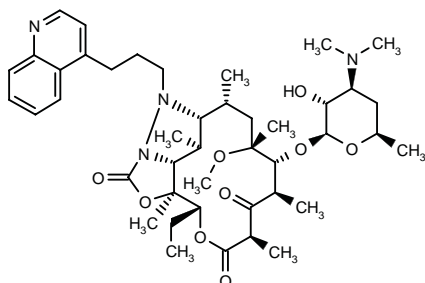


C31 H51 N3 O9; Mol wt: 609.7559

ACTION – Macrolide antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, as well as certain protozoa. Within this series of specifically claimed erythromycin derivatives, the following are also included:



271378: C31 H53 N3 O9



271379: C43 H64 N4 O9

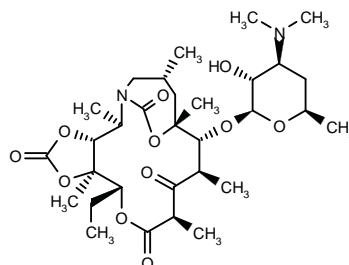
SOURCE – Pfizer.

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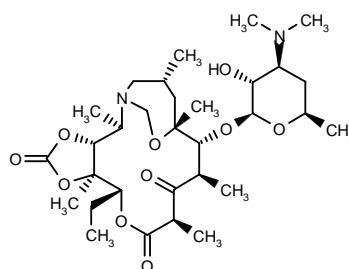
271803

9-Deoxy-3-des(hexopyranosyloxy)-3-oxo-9a-aza-9a-homoerythromycin A 11-*O*,12-*O*-cyclic carbonate, 9a-*N*,6-*O*-cyclic carbamate



C31 H50 N2 O11; Mol wt: 626.7390

ACTION – 9a-Azalide antibiotic structurally related to erythromycin A, active against Gram-positive and Gram-negative bacteria. Another specifically claimed compound from this series of 9a-aza-3-ketolides is:



271804: C31 H52 N2 O10

SOURCE – Merck & Co.

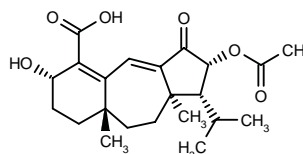
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- Blizzard, T.A. et al. (Merck & Co., Inc.) *9A-Aza-3-ketolides, compsns. containing such cpds. and methods of treatment.* WO 9900125.

CR-115

268305

(1*R*,2*R*,6*S*,8a*R*,10a*R*)-2-(Acetyloxy)-6-hydroxy-1-isopropyl-8a,10a-dimethyl-3-oxo-1,2,3,6,7,8,8a,9,10,10a-decahydrobenzo[*f*]azulene-5-carboxylic acid



C22 H30 O6; Mol wt: 390.4730

ACTION – Diterpenoid antibiotic isolated from an unidentified fungus and proven active against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium* and *Escherichia coli* imp (MIC = 8-64 mg/l). Its bactericidal activity appears to be due mainly to damage to the bacterial membrane.

SOURCE – Wyeth-Ayerst.

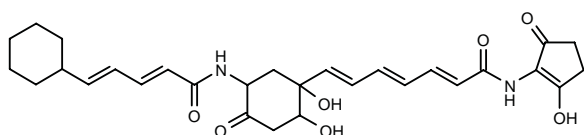
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H-4750-D₂

270996

7-[5-[5-Cyclohexyl-2(*E*),4(*E*)-pentadienoylamino]-1,2-dihydroxy-4-oxocyclohexyl]-*N*-(2-hydroxy-5-oxo-1-cyclopenten-1-yl)-2(*E*),4(*E*),6(*E*)-heptatrienamide



C29 H36 N2 O7; Mol wt: 524.6104

ACTION – Antibiotic of the manumycin group isolated from the culture of *Micropolyspora* sp. H4750, active against Gram-positive bacteria.

SOURCE – Sichuan Industrial Institute of Antibiotics, Chengdu (CN).

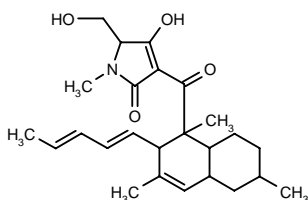
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LL-49F233α

271162

4-Hydroxy-5-(hydroxymethyl)-1-methyl-3-[1,3,6-trimethyl-2-[1(*E*),3(*E*)-pentadienyl]-1,2,4a,5,6,7,8,8a-octahydro-naphth-1-ylcarbonyl]-1,5-dihydro-2*H*-pyrrol-2-one



C25 H35 N O4; Mol wt: 413.5545

ACTION – Antibiotic extracted from an unknown fungus that is structurally different from known tetramic acid-containing compounds. It was active against methicillin-resistant *Staphylococcus aureus* (MIC = 0.5-1 mg/l) and vancomycin-resistant enterococci (MIC = 1-4 mg/l), had poor activity against wild-type Gram-negative microorganisms (MIC > 64 mg/l) but showed good activity against *Escherichia coli* imp (MIC = 2 mg/l). Structural modifications are currently being evaluated in an attempt to improve its spectrum of antibacterial activity.

SOURCE – Wyeth-Ayerst.

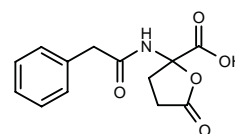
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1. Singh, M.P. et al. *LL-49F233α, a novel antibiotic produced by an unknown fungus: Biological and mechanistic activities*. J Antibiot 1998, 51(12): 1109.

ANTIBACTERIAL DRUGS

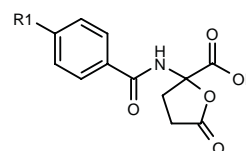
270992

5-Oxo-2-(2-phenylacetamido)tetrahydrofuran-2-carboxylic acid



C13 H13 N O5; Mol wt: 263.2477

ACTION – γ -Lactone antibacterial agent active against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Enterobacter aerogenes*. Compound displays comparable antibacterial activity to cefriaxone against most bacteria tested. Other 2-amino-5-oxo-2-tetrahydrofuran carboxylic acids include the following:



Compound	R1	Formula
270993	H	C ₁₂ H ₁₁ NO ₅
270994	Cl	C ₁₂ H ₁₀ ClNO ₅

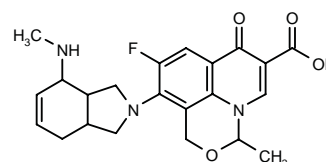
SOURCES – Sichuan Industrial Institute of Antibiotics, Chengdu (CN); West China University of Medical Sciences, Chengdu (CN).

REFERENCES

1. Li, Y.F. et al. *2-Amino-5-oxo-2-tetrahydrofuran carboxylic acids, novel γ -lactone antibacterial agents*. Chin J Antibiot 1998, 23(5): 336.

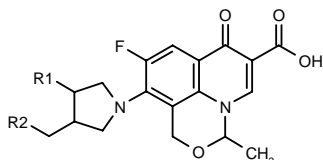
271293

9-Fluoro-3-methyl-10-[4-(methylamino)-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-2-yl]-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]-benzoxazine-6-carboxylic acid



C22 H24 F N3 O4; Mol wt: 413.4466

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria including resistant microorganisms; compound exhibited MIC values of 0.015 µg/ml or less, 0.12, 0.12, 0.12, 0.12 and 16 µg/ml, respectively, when tested against *Escherichia coli* Z 431 Lit, *Klebsiella pneumoniae* 2363 Ge, *Salmonella* 1Fr, *Enterobacter* 0,4 Ge 02-33, *Staphylococcus aureus* 3781 Ge and *Pseudomonas* BS 698 TGD. Other exemplified compounds within this series of pyrido[3,2,1-*ij*][3,1]-benzoxazine derivatives include the following:



Compound	R1,R2	Formula
271294	-CH(NH ₂)CH=CH-	C ₂₁ H ₂₂ FN ₃ O ₄
271295	-NHCH ₂ CH ₂ -	C ₂₀ H ₂₂ FN ₃ O ₄

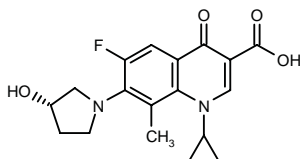
SOURCE – Bayer.

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1. Hallenbach, W. et al. (Bayer AG) *Pyrido[3,2,1-*ij*][3,1]benzoxazine derivs.* US 5854241, WO 9601829.

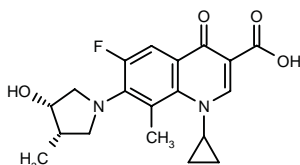
271474

1-Cyclopropyl-6-fluoro-7-[3(*S*)-hydroxypyrrolidin-1-yl]-8-methyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid



C₁₈ H₁₉ F N₂ O₄; Mol wt: 346.3561

ACTION – Quinolone antibacterial agent with activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P JC-1 (MIC = 0.006 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 0.025 µg/ml) and *Pseudomonas aeruginosa* IFO3445 (MIC = 0.20 µg/ml). Compound exhibited no toxic effects in the chromosomal aberration test and it had no proconvulsant effect in mice following i.p. administration. Another compound from this series of 7-(hydroxypyrrolidinyl)-quinolones is:



271475: C₁₉ H₂₁ F N₂ O₄

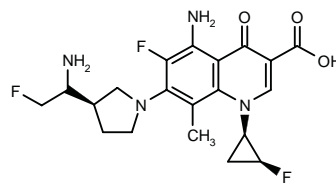
SOURCE – Hokuriku.

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1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *7-(Hydroxypyrrolidinyl)quinoline carboxylate derivs.* JP 98324686.

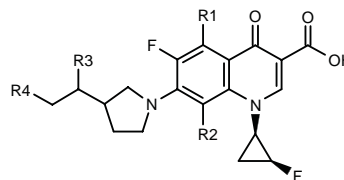
271646

5-Amino-7-[3(*R*)-(1-amino-2-fluoroethyl)pyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C₂₀ H₂₃ F₃ N₄ O₃; Mol wt: 424.4207

ACTION – Quinolone antibacterial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* 209P (MIC = 0.003 µg/ml or less) and *Escherichia coli* NIHJ (MIC = 0.003 µg/ml or less). Within this series of substituted aminomethyl pyrrolidine derivatives, the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
271647	NH ₂	OMe	NH ₂	F	3R	C ₂₀ H ₂₃ F ₃ N ₄ O ₄
271648	NH ₂	Me	NHMe	F	3R	C ₂₁ H ₂₅ F ₃ N ₄ O ₃
271650	NH ₂	OMe	NHMe	F	3R	C ₂₁ H ₂₅ F ₃ N ₄ O ₄
271651	NH ₂	F	(S)-NH ₂	OMe	(-)	C ₂₀ H ₂₃ F ₃ N ₄ O ₄
271652	H	OMe	(S)-NH ₂	OMe	(-)	C ₂₁ H ₂₅ F ₂ N ₃ O ₅
271653	NH ₂	OMe	(S)-NH ₂	OMe		C ₂₁ H ₂₆ F ₂ N ₄ O ₅
271655	NH ₂	OMe	NH ₂	CH ₂ F	3R	C ₂₁ H ₂₅ F ₃ N ₄ O ₄

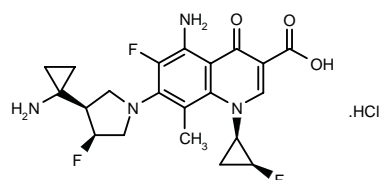
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Takemura, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *Substd. aminomethyl pyrrolidine derivs.* JP 98287669.

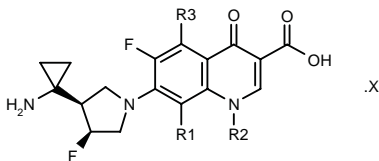
271702

5-Amino-7-[3(*R*)-(1-aminocyclopropyl)-4(*S*)-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-8-methyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid hydrochloride



C₂₁ H₂₃ F₃ N₄ O₃ . HCl; Mol wt: 472.8926

ACTION – Quinolone antibacterial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P and *Escherichia coli* NIHJ (MIC = 0.003 µg/ml or less), and low acute toxicity: no deaths were observed in mice after a single dose of 150 mg/kg i.v. Other representative compounds within this series of *cis*-disubstituted aminocycloalkyl-pyrrolidine derivatives include the following:



Compound	R1	R2	R3	X	Formula
271703	(1R,2S)-2-F-cyclopropyl	OMe	H		C ₂₁ H ₂₂ F ₃ N ₃ O ₄
271704	-(S)-OCH ₂ CH(Me)-		H	HCl	C ₂₀ H ₂₁ F ₂ N ₃ O ₄ ·HCl
271705	-(S)-OCH ₂ CH(Me)-		NH ₂		C ₂₀ H ₂₂ F ₂ N ₄ O ₄

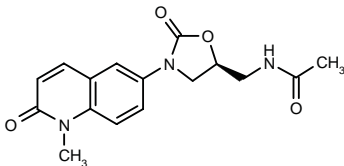
SOURCE – Daiichi Pharmaceutical.

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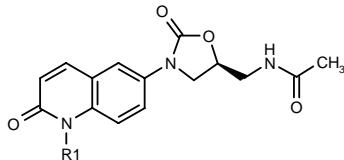
271773

N-[3-(1-Methyl-2-oxo-1,2-dihydro-6-quinolinyl)-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C16 H17 N3 O4; Mol wt: 315.3273

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria such as *Staphylococcus* 133 (MIC = 2 µg/ml) and *Staphylococcus* 9TV (MIC = 1 µg/ml). Other compounds from this series of 2-oxo- and 2-thio-1,2-dihydroquinolinyl-oxazolidinones include the following:



Compound	R1	Formula
271774	Et	C ₁₇ H ₁₉ N ₃ O ₄
271775	i-Pr	C ₁₈ H ₂₁ N ₃ O ₄
271776	CH ₂ CN	C ₁₇ H ₁₆ N ₄ O ₄
271777	CH ₂ CH ₂ OH	C ₁₇ H ₁₉ N ₃ O ₅
271778	SO ₂ Me	C ₁₆ H ₁₇ N ₃ O ₆ S

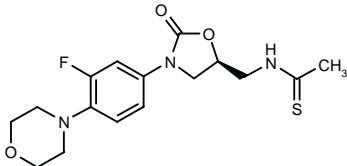
SOURCE – Bayer.

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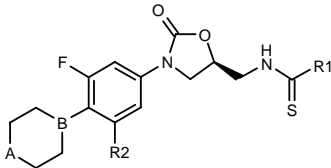
272068

N-[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



C16 H20 F N3 O3 S; Mol wt: 353.4160

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 9213 (MIC = 1 µg/ml), *Staphylococcus epidermidis* 30593 (MIC = 0.25 µg/ml), *Enterococcus faecalis* 12712 (MIC = 0.5 µg/ml), *Streptococcus pneumoniae* 9912 (MIC < 0.125 µg/ml), *Streptococcus pyogenes* 152 (MIC < 0.125 µg/ml), *Haemophilus influenzae* 30063 (MIC = 8 µg/ml) and *Moraxella catarrhalis* 30610 (MIC = 1 µg/ml). Other compounds from this series of oxazolidinone derivatives having a thiocarbonyl functionality include the following:



Compound	R1	R2	A	B	Isomer	Formula
272069	Me	H	SO	CH	trans	C ₁₇ H ₂₁ FN ₂ O ₃ S ₂
272070	Me	H	SO ₂	CH		C ₁₇ H ₂₁ FN ₂ O ₄ S ₂
272071	NH ₂	H	SO ₂	CH		C ₁₆ H ₂₀ FN ₃ O ₄ S ₂
272072	Me	H	-N(COCH ₂ OH)-	N		C ₁₈ H ₂₃ FN ₄ O ₄ S
272073	Me	F	-N(COCH ₂ OH)-	N		C ₁₈ H ₂₂ F ₂ N ₄ O ₄ S

SOURCE – Pharmacia & Upjohn.

REFERENCES

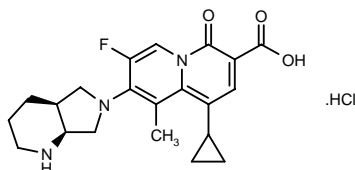
1. Hester, J.B. Jr. et al. (Pharmacia & Upjohn Co.) Oxazolidinone antibacterial agents having a thiocarbonyl functionality. WO 9854161.

ANTIMYCOBACTERIAL AGENTS

ABT-255

269254

(1*S*,6*S*)-1-Cyclopropyl-8-(2,8-diazabicyclo[4.3.0]octan-8-yl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride



C21 H24 F N3 O3 . HCl; Mol wt: 421.8975

ACTION – Oral antibacterial agent active against *Mycobacterium tuberculosis* including both drug-susceptible (MIC = 0.016-0.031 µg/ml) and rifampicin- or ethambutol-resistant strains (MIC = 0.031 µg/ml). *In vitro*, it was also effective against *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli* (MIC = 0.015, 0.03 and 0.015 µg/ml, respectively). In mouse models of acute *S. aureus* and *S. pneumoniae* infections, it showed superior efficacy to ciprofloxacin (ED₅₀ = 2.5 and 3.6 mg/kg p.o., respectively, vs. 287.2 and > 100 mg/kg p.o., respectively); comparable efficacy was seen against *E. coli* infections (ED₅₀ = 1.0 mg/kg p.o. for both drugs). In murine models of pulmonary infections caused by both drug-susceptible and drug-resistant strains of *M. tuberculosis*, 4 weeks of oral treatment with ABT-255 in the dose range of 6.25-25 mg/kg induced significant reductions in viable bacterial counts.

SOURCE – Abbott.

REFERENCES

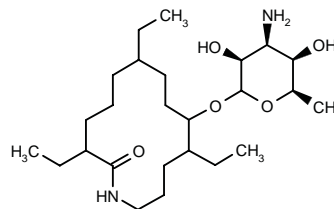
1. Chu, D.T. et al. (Abbott Laboratories Inc.) *Quinolizone type cpds.* EP 871628, WO 9639407.

2. Oleksijew, A. et al. *In vivo efficacy of ABT-255 against drug-sensitive and -resistant Mycobacterium tuberculosis strains.* Antimicrob Agents Chemother 1998, 42(10): 2674.

ANTIFUNGAL AGENTS

270554

9-(3-Amino-3,6-dideoxy-D-talopyranosyloxy)-2,6,10-triethyltridecano-13-lactam



C25 H48 N2 O5; Mol wt: 456.6632

ACTION – Macrolactam monosaccharide antimicrobial agent isolated from antimicrobial complex 517 produced by culturing the microorganism *Actinomadura vulgaris* subsp. *vulgaris* ATCC 53748. It was active *in vitro* against 7 species of *Candida* (geometric mean MIC = 2.0-6.56 µg/ml) and 6 species of dermatophytes (geometric mean MIC = 101.6 µg/ml); also reported to have antibacterial activity against Gram-positive and Gram-negative microorganisms.

SOURCE – Schering-Plough.

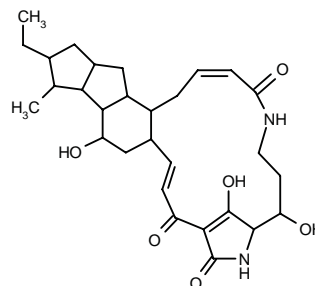
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1. Hegde, V.R. et al. (Schering Corp.) *Actinomadura vulgaris subsp vulgaris and antimicrobial complex and antimicrobial.* US 5837691.

AFA-0520

270976

(2*Z*,14*E*)-19-Ethyl-8,17,22-trihydroxy-18-methyl-4,5,6,7,8,9,10,11,12,13,15a,16,17,17a,17b,18,19,20,20a,21,21a,21b-docosahydro-1*H*-9,12-methenocyclopent-[1,2]indeno[4,5-*k*][1,6]diazacycloheptadecine-4,11,13-trione



C29 H40 N2 O6; Mol wt: 512.6430

ACTION – Antifungal agent isolated from the microorganism *Streptomyces* sp. TA-0364 (FERM P-16190); it was active *in vitro* against various fungi including *Cryptococcus neoformans* TIMM0354 (MIC = 6.25 µg/ml), *Candida albicans* YA-26089 (MIC = 6.25 µg/ml), *Candida tropicalis* JCM1541 (MIC = 12.5 µg/ml) and *Aspergillus fumigatus* TIMM0064 (MIC = 25 µg/ml).

SOURCE – Taisho.

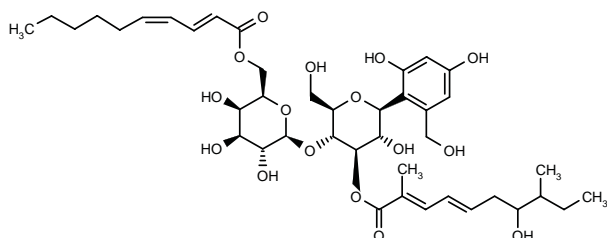
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1. Sugawara, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Anti-fungal cpds.* JP 98310584.

CORYNECANDIN

260279

4-[4-O-[6-O-[Deca-2(*E*),4(*Z*)-dienoyl]-β-D-galactopyranosyl]-3-O-[7-hydroxy-2,8-dimethyldeca-2(*E*),4(*Z*)-dienoyl]-β-D-glucopyranosyl]-5-(hydroxy-methyl)resorcinol



C41 H60 O16; Mol wt: 808.9090

ACTION – Antifungal glycolipid isolated from a culture of the fungus *Coryneum modonium* strain AB 2020T-223 (NRRL 25349), with comparable activity against *Candida albicans* CCH 442 to fusacandin, papulacandin B, cilofungin and amphotericin B (MIC = 0.98, 1.96, 1.96, 0.98 and 0.48 μg/ml, respectively) in the absence of sorbitol; sorbitol rescue of cell growth indicated that it inhibits fungal cell wall synthesis and assembly, and compound was shown to inhibit β-(1,3)-glucan synthesis *in vitro* with an IC₅₀ value of 12.9 μg/ml (IC₅₀ = 25.0, 1.9 and 52.0 μg/ml, respectively, for fusacandin, papulacandin B and cilofungin).

SOURCE – Abbott.

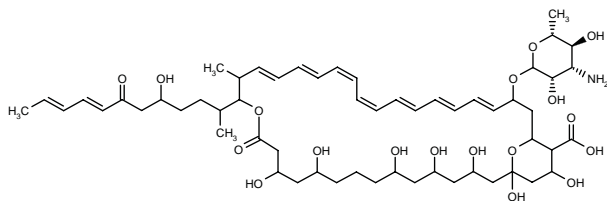
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1. Gunawardana, G.P. et al. (Abbott Laboratories Inc.) *Antifungal corynecandin.* US 5863773.
2. *Corynecandin: A novel antifungal glycolipid from Coryneum modonium.* J Antibiot 1997, 50(10): 884.

3874 H3

269612

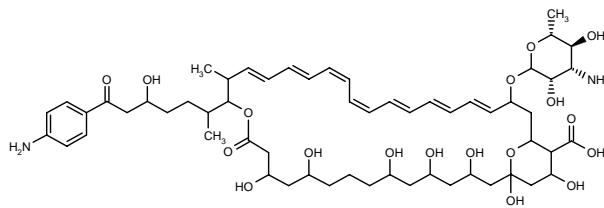
1,3,5,7,11,13,37-Heptahydroxy-17-(4-hydroxy-1-methyl-6-oxo-7,9-undecadienyl)-33-(D-mannopyran-oxyl)-18-methyl-15-oxo-16,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid



C58 H86 N2 O18; Mol wt: 1099.3130

Yellow amphoteric powder, $[\alpha]_D^{21} +128^\circ$ (c 0.30, MeOH).

ACTION – Antifungal heptaene antibiotic produced by *Streptomyces* sp. HAG 003874, with broad-spectrum activity including yeasts, dermatophytes and filamentous fungi. Compound showed comparable or slightly superior activity to amphotericin B against a range of fungi including *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Cryptococcus neoformans*, *Aspergillus niger*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Trichophyton interdigitalis* (MIC = 0.12-0.5 μg/ml). 3874 H3 exhibited significantly greater hemolytic activity in human blood than amphotericin B (30% at 100 mg/l vs. 3% for amphotericin B). Another compound from this same source –3874 H1– displayed better antifungal potency but was significantly more toxic in the brine shrimp model compared to 3874 H3 or amphotericin B.



3874 H1 [269611]: C58 H86 N2 O18

SOURCE – Hoechst Marion Roussel.

REFERENCES

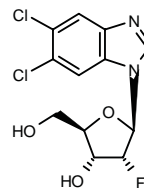
1. Vértessy, L. et al. (Hoechst AG) *Polyene antibiotics, 3874 H1 to H6, method for their preparation and use.* EP 829486, EP 829487.
2. Vértessy, L. et al. *3874 H1 and H3, novel antifungal heptaene antibiotics produced by Streptomyces sp. HAG 003874.* J Antibiot 1998, 51(10): 921.

ANTIVIRAL DRUGS

270545

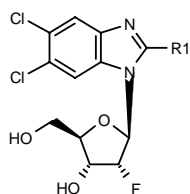
270545

5,6-Dichloro-1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)-1*H*-benzimidazole



C12 H11 Cl2 F N2 O3; Mol wt: 321.1339

ACTION – Antiviral agent with potent *in vitro* activity against human cytomegalovirus (HCMV; IC₅₀ = 12.5 ± 0.7 μM) and low cytotoxicity against uninfected MRC5 cells (IC₅₀ >100 μM). Other specifically claimed modified benzimidazole nucleosides include the following:



Compound	R1	Formula
270546	Br	C ₁₂ H ₁₀ BrCl ₂ FN ₂ O ₃
270547	i-PrNH	C ₁₈ H ₁₈ Cl ₂ FN ₃ O ₃

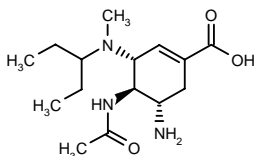
SOURCES – Glaxo Wellcome; University of Michigan, Ann Arbor, MI (US).

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1. Townsend, L.B. et al. (University of Michigan; Glaxo Wellcome Inc.) *Modified benzimidazole nucleosides as antiviral agents*. US 5840743.

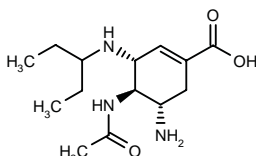
270689

(3*R*,4*R*,5*S*)-4-(Acetamido)-5-amino-3-[*N*-(1-ethylpropyl)-*N*-methylamino]-1-cyclohexene-1-carboxylic acid



C₁₅ H₂₇ N₃ O₃; Mol wt: 297.3963

ACTION – Antiviral agent, an inhibitor of influenza A neuraminidase (sialidase; IC₅₀ = 6 nM) with comparable activity to GS-4071. Another compound from this series of C3-aza carbocyclic compounds is:



270690: C₁₄ H₂₅ N₃ O₃

SOURCE – Gilead.

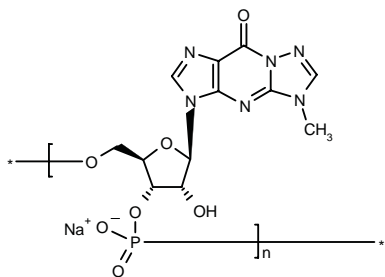
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PTPR

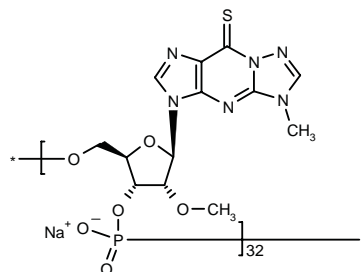
270816

Poly(3'→5')-5-Methyl-3-(β-D-ribofuranosyl)-5,9-dihydro-3*H*-[1,2,4]triazolo[1,5-*a*]purin-9-one 3'-phosphate sodium salt



(C₁₂ H₁₂ N₆ Na O₇ P)_n

ACTION – Antiviral agent, a high-molecular-weight polynucleotide with potent inhibitory activity against human cytomegalovirus (HCMV; IC₅₀ = 0.43 μM against strain AD-169) and HIV (IC₅₀ = 1.0 μM against strain IIIB), low cytotoxicity (CD₅₀ > 2.5 μM in CEM-SS cells; CD₅₀ > 7.9 μM in MRC-5 cells) and a good therapeutic index. Another related oligonucleotide with a similar profile is:



TTPR [270817]: C₄₁₆ H₄₄₈ N₁₉₂ Na₃₂ O₁₉₂ P₃₂ S₃₂

SOURCES – Aral Biosynthetics; Southern Research Institute, Frederick MD (US); University of Utah, Salt Lake City, UT (US).

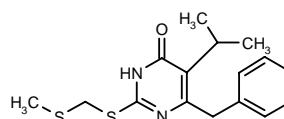
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1. Tutonda, M.G. et al. *Antiviral oligo- and polyribonucleotides containing selected triazolo[2,3-*a*]purines*. J Med Chem 1998, 41(25): 4958.

AIDS MEDICINES

265590

6-Benzyl-5-isopropyl-2-(methylsulfanylmethylsulfanyl)-pyrimidin-4(3*H*)-one



C₁₆ H₂₀ N₂ O S₂; Mol wt: 320.4790

ACTION – Antiviral agent for AIDS, a potent non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) from a series of dihydroalkoxybenzoxypyrimidine (DABO) derivatives; it inhibited recombinant enzyme with an IC₅₀ of 6.1 μM. Potent inhibition of HIV replication, as measured by p24 production, was obtained in infected human peripheral blood mononuclear cells (IC₅₀ < 1 nM), with slightly better activity compared to zidovudine (AZT) and MKC-442, whereas no cytotoxicity was detected at concentrations of > 100 μM.

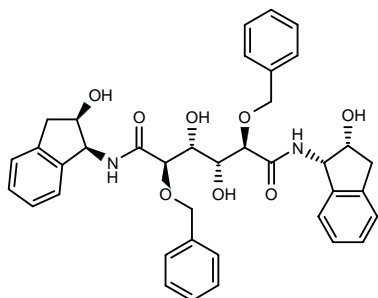
SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

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1. Sudbeck, E.A. et al. *Structure-based design of novel dihydroalkoxybenzoxypyrimidine derivatives as potent nonnucleoside inhibitors of the human immunodeficiency virus reverse transcriptase*. Antimicrob Agents Chemother 1998, 42(12): 3225.
2. Vig, R. et al. *5-Alkyl-2-[(methylthiomethyl)thio]-6-(benzyl)-pyrimidin-4-(1*H*)-ones as potent non-nucleoside reverse transcriptase inhibitors of S-DABO series*. Bioorg Med Chem Lett 1998, 8(12): 1461.

269045

(2*R*,3*R*,4*R*,5*R*)-2,5-Di(benzyloxy)-3,4-dihydroxy-*N,N'*-bis[2(*R*)-hydroxyindan-1(*S*)-yl]hexanediamide



C38 H40 N2 O8; Mol wt: 652.7400

ACTION – Antiviral agent for AIDS, a potent HIV-1 protease inhibitor ($K_i = 0.2$ nM) with good anti-HIV-1 activity in MT-4 cells ($ED_{50} = 0.06$ µg/ml) comparable to that of ritonavir and indinavir ($ED_{50} = 0.05$ and 0.04 µg/ml, respectively). Further studies on this compound are currently in progress.

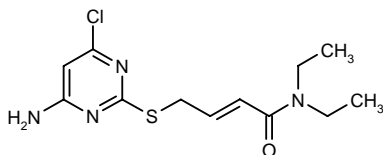
SOURCES – Linköping University, Linköping (SE); Stockholm University, Stockholm (SE); Uppsala University, Uppsala (SE); .

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1. Alterman, M. et al. *Design and synthesis of new potent C2-symmetric HIV-1 protease inhibitors. Use of L-mannaric acid as a peptidomimetic scaffold.* J Med Chem 1998, 41(20): 3782.

269048

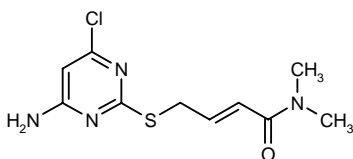
4-(4-Amino-6-chloropyrimidin-2-ylsulfanyl)-*N,N*-diethyl-2(*E*)-butenamide



C12 H17 Cl N4 O S; Mol wt: 300.8123

M.p. 143-5 °C.

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with *in vitro* activity against both wild-type and delavirdine-resistant RT ($IC_{50} = 60$ and 50 nM, respectively). In infected MT-4 cells, compound inhibited the replication of both wild-type and delavirdine-resistant HIV-1 with IC_{90} values of 20 and 110 nM, respectively. Another compound within this series of pyrimidine thioesters is:



269046: C10 H13 Cl N4 OS

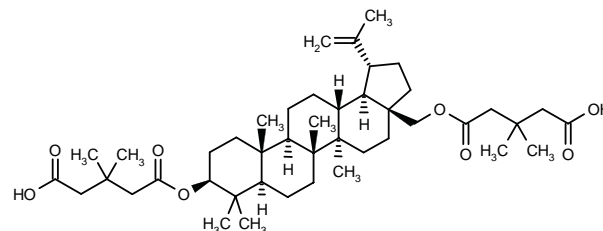
SOURCE – Pharmacia & Upjohn.

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2. Nugent, R.A. et al. *Pyrimidine thioethers: A novel class of HIV-1 reverse transcriptase inhibitors with activity against BHAP-resistant HIV.* J Med Chem 1998, 41(20): 3793.

270372

Bis(3,3-dimethylglutaric acid) 3β,28-dihydroxylup-20(29)-en-3,28-diyl diester



C44 H70 O8; Mol wt: 727.0290

Off-white amorphous powder, $[\alpha]_D^{25} +21.9^\circ$ (c 0.2, CHCl₃).

ACTION – Antiviral agent for AIDS, a betuline derivative with subnanomolar anti-HIV-1 activity ($EC_{50} = 0.6$ nM in H9 cells) and a high therapeutic index ($IC_{50} = 14.2$ µM in uninfected cells; TI = 21,515) similar to AZT. Compound appears to inhibit HIV replication at a late stage in the viral life cycle following protein synthesis.

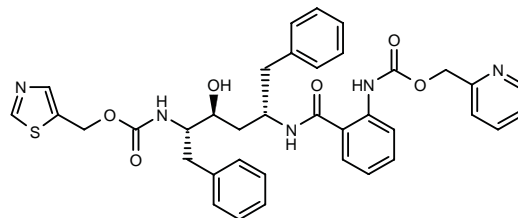
SOURCES – Biotech Research Laboratories; University of North Carolina at Chapel Hill, Chapel Hill, NC (US).

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2. Sun, I.-C. et al. *Anti-AIDS agents. 34. Synthesis and structure-activity relationships of betulin derivatives as anti-HIV agents.* J Med Chem 1998, 41(23): 4648.

271184

(1*S*,2*S*,4*S*)-*N*-[1,4-Dibenzyl-2-hydroxy-4-[2-(2-pyridinylmethoxycarboxamido)benzamido]butyl]carbamic acid thiazol-5-ylmethyl ester



C37 H37 N5 O6 S; Mol wt: 679.7943

ACTION – Antiviral agent for AIDS, an unsymmetrical anthranilamide-containing HIV-1 protease inhibitor ($K_i = 0.03$ nM) with potent *in vitro* antiviral activity ($EC_{50} = 0.2$ µM). Compound showed good oral bioavailability in rats: peak plasma levels after a single oral dose of 40 mg/kg were over 30-fold higher than the antiviral EC_{50} , with a half-life of > 8 h.

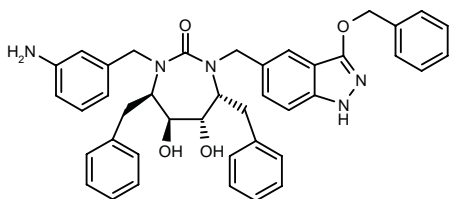
SOURCE – National Cancer Institute (US).

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1. Randad, R.S. et al. *Unsymmetric nonpeptidic HIV protease inhibitors containing anthranilamide as a P2' ligand*. Bioorg Med Chem Lett 1998, 8(24): 3537.

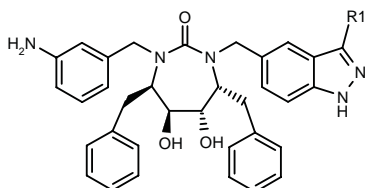
271424

(4*R*,5*S*,6*S*,7*R*)-1-(3-Aminobenzyl)-4,7-dibenzyl-3-[3-(benzyloxy)-1*H*-indazol-5-ylmethyl]-5,6-dihydroxy-1,3-diazepan-2-one



C41 H41 N5 O4; Mol wt: 667.8059

ACTION – Antiviral agent for AIDS, an inhibitor of HIV protease. A representative compound from a series of indazoles of cyclic ureas, wherein the following are also included:



Compound	R1	Formula
271425	2-NH2-PhO	C ₄₀ H ₄₀ N ₆ O ₄
271426	1-pyrazolyl	C ₃₇ H ₃₇ N ₇ O ₃
271428	4-NH2-1-pyrazolyl	C ₃₇ H ₃₈ N ₆ O ₃
271430	2-F-PhCONH	C ₄₁ H ₃₉ FN ₆ O ₄
271432	4-CN-PhO	C ₄₁ H ₃₈ N ₆ O ₄
271433	2-F-PhO	C ₄₀ H ₃₈ FN ₅ O ₄
271434	3-Ac-PhO	C ₄₂ H ₄₁ N ₅ O ₅

SOURCE – DuPont Pharmaceuticals.

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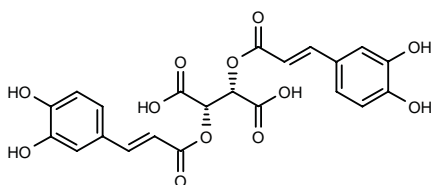
1. Rodgers, J.D. et al. (DuPont Pharmaceuticals Co.) *Indazoles of cyclic ureas useful as HIV protease inhibitors*. WO 9843969.

L-CHICORIC ACID

270281

(2*R*,3*R*)-Bis[3-(3,4-dihydroxyphenyl)-2(*E*)-propenoyloxy]-butanedioic acid

(–)-Chicoric acid



C22 H18 O12; Mol wt: 474.3722

ACTION – Antiviral agent for AIDS, a selective inhibitor of HIV-1 integrase (IC₅₀ ~100 nM). Combination of this first-generation HIV integrase inhibitor with a protease inhibitor and zidovudine allowed a greater than 33% reduction in the concentrations of protease inhibitor and zidovudine required for an equivalent anti-HIV effect.

SOURCE – University of California, Irvine, CA (US).

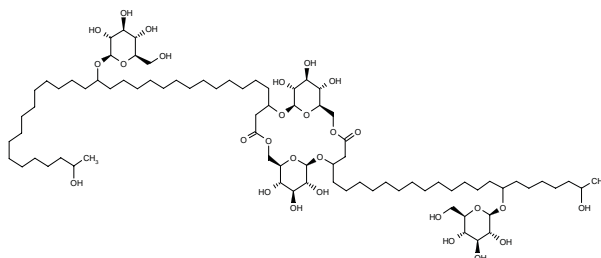
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4. Zhao, H. and Burke, T.R. Jr. *Facile syntheses of (2*R*,3*R*)-(-) and (2*S*,3*S*)-(+)-chicoric acids*. Synth Commun 1998, 28(4): 737.

FATTIVIRACIN A1

270412

3-[6-*O*-[3,17-Bis(β-D-glucopyranosyloxy)-1-oxotetracosyl]-β-D-glucopyranosyloxy]-17-(β-D-glucopyranosyloxy)-32-hydroxytritriacontanoic acid intramolecular ester



C81 H150 O28; Mol wt: 1572.0480

Colorless oil, [α]_D¹⁹ –19.1° (c 0.1, MeOH).

ACTION – Antiviral agent isolated from the culture filtrate of *Streptomyces microflavus* strain no. 2445, with broad-spectrum activity against enveloped viruses including HIV. Compound was active against herpes simplex virus type 1 (HSV-1; EC₅₀ = 3.88 μg/ml), varicella-zoster virus (EC₅₀ = 3.37 μg/ml), influenza A virus (EC₅₀ = 2.05 μg/ml) and HIV-1 (EC₅₀ = 10.35 μg/ml), and it showed no cytotoxicity against Vero cells at up to 3.75 mg/ml. It appears to act by inactivating viral particles and inhibiting viral entry into host cells.

SOURCE – Kumamoto University, Kumamoto (JP).

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1. Uyeda, M. et al. *Fattiviracin A1, a novel antiviral agent produced by Streptomyces microflavus strain No. 2445. I. Taxonomy, fermentation, isolation, physico-chemical properties and structure elucidation*. J Antibiot 1998, 51(9): 823.
2. Yokomizo, K. et al. *Fattiviracin A1, a novel antiviral agent produced by Streptomyces microflavus strain No. 2445. II. Biological properties*. J Antibiot 1998, 51(11): 1035.

PRO-2000

212502

Naphthalene sulfonate polymer with a molecular weight of 5 kDa

ACTION – Antiviral agent for AIDS, a naphthalene sulfonate polymer particularly suited for use as a vaginal microbicide for preventing HIV-1 transmission. It suppresses HIV-1 replication by blocking the binding of the viral envelope glycoprotein gp120 to the CD4 receptor ($IC_{50} = 0.4 \mu\text{g/ml}$). Compound suppresses the replication of a range of HIV-1 isolates in a variety of cell types including macrophages. It is also reported to prevent genital herpes simplex virus type 2 (HSV-2) infection. Repeated application of an intravaginal gel containing 0.1, 1.0 or 4.0% PRO-2000 was not associated with vaginal irritation in female rabbits and no drug was detectable in plasma. Phase I safety studies in healthy volunteers have also demonstrated good tolerability.

SOURCES – Medical Research Council; Procept.

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- Wortel, C.H. et al. *Tolerance and pharmacokinetics of a new antiviral agent in healthy, HIV-negative volunteers*. 11th Int Conf AIDS (July 7-12, Vancouver) 1996, Abst We.B.3129.
- Wright, A. et al. *Safety and tolerability of PRO 2000 gel: A potential vaginal virucide*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 227.
- NIAID to sponsor trials of female-controlled topical microbicide; FDA gives green light to study*. *Prous Science Daily Essentials* 1998, Nov 5.
- Phase I clinical trial for topical microbicide initiated in London*. Procept, Inc. Press Release 1997, Jan 21.
- PRO-2000 gel well tolerated in phase I trial in healthy females*. *Prous Science Daily Essentials* 1998, Feb 4.
- Procept allocates funds for further development of PRO-2000*. *Prous Science Daily Essentials* 1998, April 22.
- Procept and British Medical Research Council sign collaborative agreement*. Procept, Inc. Press Release 1996, Oct 30.
- Procept begins phase I/II clinical trial for PRO 2000 in HIV-positive patients*. Procept, Inc. Press Release 1995, Aug 24.
- Procept completes phase I testing with PRO-2000 gel*. *Prous Science Daily Essentials* 1997, Oct 22.
- Procept completes phase I trial of PRO-2000 gel*. *Prous Science Daily Essentials* 1997, June 3.
- Procept initiates new phase I/II clinical trial for PRO 2000 in HIV-positive patients*. Procept, Inc. Press Release 1996, Jan 9.
- Procept initiates phase I clinical trial of topical microbicide*. Procept, Inc. Press Release 1996, Dec 9.

18. *Procept to develop gel to prevent sexual transmission of HIV in women. Key preclinical results presented at AIDS conference*. Procept, Inc. Press Release 1996, Sept 10.

19. *Procept's PRO 2000 Gel provides protection against herpes infection in mice; findings to be presented at 12th World AIDS Conference in Geneva*. Procept, Inc. Press Release 1998, June 3.

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21. *Procept's PRO-2000 gel protects against herpes infection in mice*. *Prous Science Daily Essentials* 1998, June 9.

22. *Procept's PRO-2000 Gel shows positive results in protection from HIV infection*. *Prous Science Daily Essentials* 1999, March 12.

23. *Procept's topical microbicide shown to be contraceptive*. *Prous Science Daily Essentials* 1997, May 12.

24. *Procept, Pacific Pharmaceuticals move closer to merger*. *Prous Science Daily Essentials* 1998, Dec 15.

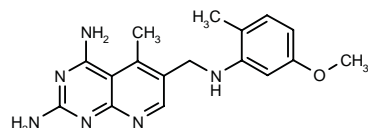
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SRI-8202

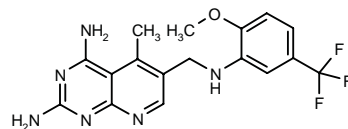
271169

6-(5-Methoxy-2-methylphenylaminomethyl)-5-methylpyrido[2,3-d]pyrimidine-2,4-diamine



C17 H20 N6 O; Mol wt: 324.3860

ACTION – Dihydrofolate reductase (DHFR) inhibitor with similar potency and significantly improved selectivity for microbial enzymes ($IC_{50} = 0.038$ and $0.023 \mu\text{M}$, respectively, against enzyme from *Pneumocystis carinii* and *Toxoplasma gondii*) relative to mammalian enzyme ($IC_{50} = 0.15 \mu\text{M}$ against enzyme from rat liver) compared to trimetrexate and piritrexim. It inhibited the growth of *T. gondii* with an IC_{50} of $0.03 \mu\text{M}$. Compound was also active against DHFR from *Mycobacterium avium* ($I_{50} = 2 \text{ nM}$ vs. 400 nM for trimethoprim) and displayed activity against *Mycobacterium tuberculosis* H37Rv and H37Ra (MIC = 6.25 and $1.28\text{--}12.8 \text{ mg/l}$, respectively), as well as *M. avium* clinical isolates (MIC = 0.128 mg/l or less). Potentially useful for the treatment or prevention of opportunistic infections in AIDS patients. Another compound from this series of lipophilic antifolates is:



SRI-8228 [271170]: C17 H17 F3 N6 O

SOURCE – Southern Research Institute, Birmingham, AL (US).

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1. Piper, J.R. et al. *Lipophilic antifolates as agents against opportunistic infections. 1. Agents superior to trimetrexate and piritrexim against Toxoplasma gondii and Pneumocystis carinii in vitro evaluations.* J Med Chem 1996, 39(6): 1271.

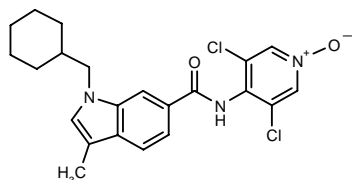
2. Suling, W.J. et al. *Susceptibilities of Mycobacterium tuberculosis and Mycobacterium avium complex to lipophilic deazapteridine derivatives, inhibitors of dihydrofolate reductase.* J Antimicrob Chemother 1998, 42(6): 811.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

270083

1-(Cyclohexylmethyl)-N-(3,5-dichloro-1-oxidopyridin-4-yl)-3-methylindole-6-carboxamide



C22 H23 Cl2 N3 O2; Mol wt: 432.3487

ACTION – Potent, orally active inhibitor of type 4 phosphodiesterase (PDE4; IC_{50} = 30 nM) with increased selectivity relative to the rolipram binding site (K_i = 86 nM) compared to rolipram (IC_{50} PDE4 = 320 nM; K_i rolipram = 4.5 nM) and RP-73401 (IC_{50} PDE4 = 1 nM; K_i rolipram = 0.4 nM). Compound inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF- α) production in mice with an ED_{50} of 7.1 mg/kg p.o. It did not induce emesis in dogs at a dose of 0.8 mg/kg i.v., whereas rolipram and RP-73401 induced emesis in all animals tested at doses of 0.03 and 0.6 mg/kg i.v., respectively. In the streptococcal cell wall-induced arthritis model in rats, it was equiactive to RP-73401 (ED_{50} = 23 and 20 mg/kg b.i.d. p.o., respectively) in inhibiting joint swelling, indicating disease-modifying effects. The good oral bioavailability (96%) and improved safety profile over other PDE4 inhibitors make this compound a promising development candidate for the treatment of rheumatoid arthritis, as well as asthma and septic shock.

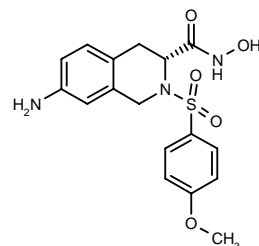
SOURCE – Rhône-Poulenc Rorer.

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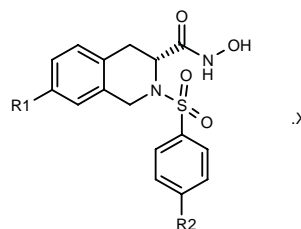
270512

7-Amino-2-(4-methoxyphenylsulfonyl)-1,2,3,4-tetrahydro-3(R)-isoquinolinecarboxhydroxamic acid



C17 H19 N3 O5 S; Mol wt: 377.4191

ACTION – Agent for the treatment of arthritis, inflammatory disorders and neoplastic diseases, among others, that acts as an inhibitor of matrix metalloproteinases (MMPs) including human stromelysin (MMP-3; IC_{50} = 10 nM) and neutrophil collagenase (MMP-8; IC_{50} = 2 nM). Other representative compounds within this series of substituted 6- and 7-amino-tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	X	Formula
270513	t-BuOCONH	OMe		C ₂₂ H ₂₇ N ₃ O ₇ S
270514	NO2	OMe		C ₁₇ H ₁₇ N ₃ O ₇ S
270515	NH2	4-F-Ph	HCl	C ₂₂ H ₂₀ FN ₃ O ₄ S.HCl
270516	t-BuOCO-L-Ala-NH	OMe		C ₂₅ H ₃₂ N ₄ O ₈ S
270517	H-L-Ala-NH	OMe	HCl	C ₂₀ H ₂₄ N ₄ O ₆ S.HCl
270518	NHCOCH2CH2CO2Na ⁺	OMe		C ₂₁ H ₂₂ N ₃ NaO ₆ S

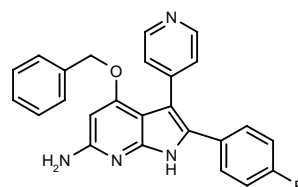
SOURCE – Hoechst Marion Roussel.

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1. Schudok, M. (Hoechst AG) *Substd. 6- and 7-aminotetrahydroisoquinolinecarboxylic acids.* EP 878467, JP 98316662.

270691

4-(Benzyloxy)-2-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



C25 H19 F N4 O; Mol wt: 410.4501

REFERENCES

1. Piper, J.R. et al. *Lipophilic antifolates as agents against opportunistic infections. 1. Agents superior to trimetrexate and piritrexim against Toxoplasma gondii and Pneumocystis carinii in vitro evaluations.* J Med Chem 1996, 39(6): 1271.

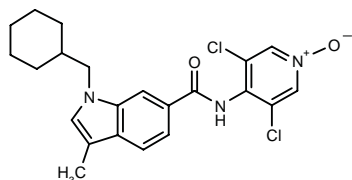
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

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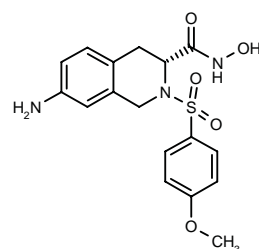
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

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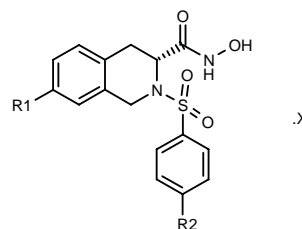
270512

7-Amino-2-(4-methoxyphenylsulfonyl)-1,2,3,4-tetrahydro-3(R)-isoquinolinecarboxhydroxamic acid



C17 H19 N3 O5 S; Mol wt: 377.4191

ACTION – Agent for the treatment of arthritis, inflammatory disorders and neoplastic diseases, among others, that acts as an inhibitor of matrix metalloproteinases (MMPs) including human stromelysin (MMP-3; $IC_{50} = 10$ nM) and neutrophil collagenase (MMP-8; $IC_{50} = 2$ nM). Other representative compounds within this series of substituted 6- and 7-amino-tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	X	Formula
270513	t-BuOCONH	OMe		C ₂₂ H ₂₇ N ₃ O ₇ S
270514	NO2	OMe		C ₁₇ H ₁₇ N ₃ O ₇ S
270515	NH2	4-F-Ph	HCl	C ₂₂ H ₂₀ FN ₃ O ₄ S.HCl
270516	t-BuOCO-L-Ala-NH	OMe		C ₂₅ H ₃₂ N ₄ O ₈ S
270517	H-L-Ala-NH	OMe	HCl	C ₂₀ H ₂₄ N ₄ O ₆ S.HCl
270518	NHCOCH2CH2CO2Na ⁺	OMe		C ₂₁ H ₂₂ N ₃ NaO ₆ S

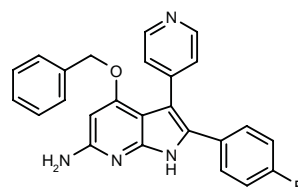
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Schudok, M. (Hoechst AG) *Substd. 6- and 7-aminotetrahydroisoquinolinecarboxylic acids.* EP 878467, JP 98316662.

270691

4-(Benzyloxy)-2-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



C25 H19 F N4 O; Mol wt: 410.4501

ACTION – Potent inhibitor of mitogen-activated protein (MAP) kinase p38 shown to inhibit tumor necrosis factor (TNF- α) production by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs) with an IC_{50} of 0.91 nM; it was about 25 times more potent than SB-203580 in this assay. Potentially useful for the treatment of inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis.

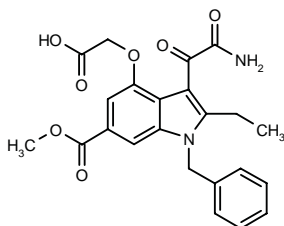
SOURCE – R.W. Johnson.

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2. Henry, J.R. et al. *Potent inhibitors of the MAP kinase p38*. Bioorg Med Chem Lett 1998, 8(23): 3335.

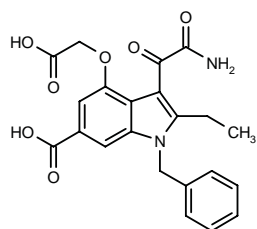
271009

2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-6-(methoxycarbonyl)-1H-indol-4-yl]oxy]acetic acid



C23 H22 N2 O7; Mol wt: 438.4338

ACTION – Water-soluble inhibitor of soluble phospholipase A_2 (sPLA $_2$; IC_{50} = 1.7 nM using human enzyme). Another representative compound within this series of indole dicarboxylic acid derivatives is:



271010: C22 H20 N2 O7

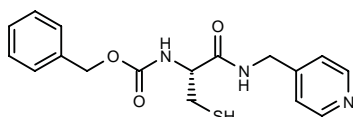
SOURCE – Shionogi.

REFERENCES

1. Ohtani, M. and Hagishita, S. (Shionogi & Co. Ltd.) *Indole dicarboxylic acid derivs*. WO 9837069.

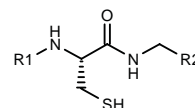
271038

N^{α} -(Benzyloxycarbonyl)- N^1 -(4-pyridylmethyl)-L-cysteinamide



C17 H19 N3 O3 S; Mol wt: 345.4211

ACTION – Antiarthritic agent that acts as an inhibitor of matrix metalloproteinases (MMPs) including human neutrophil collagenase (MMP-8; K_i = 0.71 μ M) and stromelysin (MMP-3; K_i = 4.9 μ M). Other representative cysteine derivatives include the following:



Compound	R1	R2	Formula
271039	CO ₂ CH ₂ Ph	3-Pyr	C ₁₇ H ₁₉ N ₃ O ₃ S
271040	CO ₂ CH ₂ Ph	2-Pyr	C ₁₇ H ₁₉ N ₃ O ₃ S
271041	COPh	Ph	C ₁₇ H ₁₈ N ₂ O ₂ S
271042	4-Me-PhSO ₂	Ph	C ₁₇ H ₂₀ N ₂ O ₃ S ₂

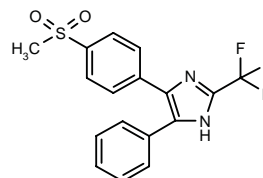
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1. Müller, J.C.D. et al. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.) *New cysteine derivs., processes for their production, and pharmaceuticals containing them*. WO 9850351.

271176

4-[4-(Methylsulfonyl)phenyl]-5-phenyl-2-(trifluoromethyl)-1H-imidazole



C17 H13 F3 N2 O2 S; Mol wt: 366.3617

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), with an IC_{50} value of 0.69 μ M for inhibition of human recombinant COX-2 and over 2000-fold selectivity versus COX-1. Although it was somewhat less potent than celecoxib in enzyme assays, compound exhibited comparable antiinflammatory activity to celecoxib, giving ED_{50} values of 0.38 and 0.16 mg/kg, respectively, in the mouse air pouch and rat adjuvant arthritis models (celecoxib ED_{50} = 0.33 and 0.37 mg/kg, respectively).

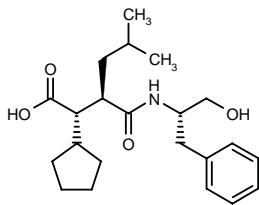
SOURCE – Searle.

REFERENCES

1. Weier, R.M. et al. (G.D. Searle & Co.) *4,5-Subst. imidazolyl cpds. for the treatment of inflammation*. EP 772601, US 5620999, WO 9603387.
2. Barta, T.E. et al. *Antiinflammatory 4,5-diarylimidazoles as selective cyclooxygenase inhibitors*. Bioorg Med Chem Lett 1998, 8(24): 3443.

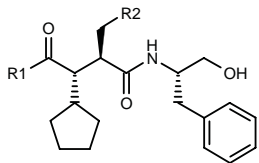
271370

(2*S*,3*R*)-3-[*N*-[1(*S*)-Benzyl-2-hydroxyethyl]carbamoyl]-2-cyclopentyl-5-methylhexanoic acid



C22 H33 N O4; Mol wt: 375.5057

ACTION – Matrix metalloproteinase (MMP) inhibitor for the treatment of rheumatoid arthritis, neuroinflammatory disorders and tumor invasion by secondary metastases. Within this series of specifically claimed hydroxamic acid and carboxylic acid derivatives, the following are also included:



Compound	R1	R2	Formula
271371	OH	4-Ph-PhCH2CH2	C ₃₃ H ₃₉ NO ₄
271372	NHOH	i-Pr	C ₂₂ H ₃₄ N ₂ O ₄
271373	NHOH	4-Ph-PhCH2CH2	C ₃₃ H ₄₀ N ₂ O ₄

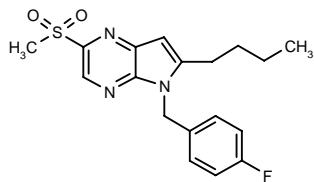
SOURCE – British Biotech.

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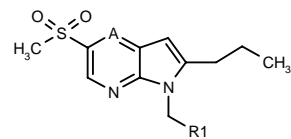
271436

6-Butyl-5-(4-fluorobenzyl)-2-(methylsulfonyl)-5*H*-pyrrolo-[2,3-*b*]pyrazine



C18 H20 F N3 O2 S; Mol wt: 361.4390

ACTION – Analgesic and antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.2 μM vs. > 20 μM for COX-1). Within this series of indole derivatives and mono- and diazaindole derivatives, the following are also included:



Compound	R1	A	Formula
271437	4-F-Ph	CH	C ₁₈ H ₁₉ FN ₂ O ₂ S
271438	4-MeO-Ph	CH	C ₁₉ H ₂₂ N ₂ O ₃ S
271439	cyclohexyl	CH	C ₁₈ H ₂₆ N ₂ O ₂ S
271440	4-F-Ph	N	C ₁₇ H ₁₈ FN ₃ O ₂ S
271441	cyclohexyl	N	C ₁₇ H ₂₅ N ₃ O ₂ S

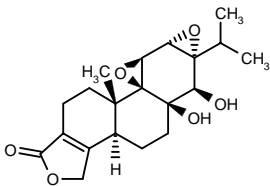
SOURCE – Chugai.

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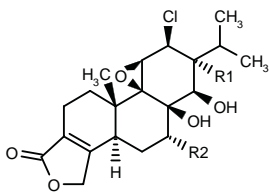
271614

[3*bS*-(3*b*α,5*a*β,6*a*β,7α,8α,9β,9*a*β,9*b*β)]-7,8:9,9*a*-Diepoxy-5*a*,6-dihydroxy-7-isopropyl-9*b*-methyl-1,3,3*b*,4,5,5*a*,6,7,8,9,9*a*,9*b*,10,11-tetradecahydrophen-anthro-[1,2-*c*]furan-1-one



C20 H26 O6; Mol wt: 362.4194

ACTION – Immunosuppressant and antiinflammatory agent, a derivative of triptolide with comparable inhibitory activity on IL-2 production (IC₅₀ = 36 ng/ml vs. 1-3 ng/ml for triptolide in Jurkat E6-1 cells) and reduced cytotoxicity, as demonstrated in an MTT assay using the same cell line (IC₅₀ = 300-500 ng/ml vs. 5 ng/ml for triptolide), thus exhibiting an improved therapeutic index (ratio MTT/IL-2 = 8-14 vs. 2-4 for triptolide). Antiinflammatory activity was demonstrated in the adjuvant-induced arthritis model in rats, where it produced 90% inhibition at 10 mg/kg/day i.p. compared to 76% inhibition for triptolide at 0.8 mg/kg/day i.p., 100% inhibition for ciclosporin at 10 mg/kg/day i.p. and 100% inhibition for prednisolone at 15 mg/kg/day i.p.; in this test, animals treated with compound, and to a lesser extent with ciclosporin, exhibited a body weight gain comparable to normal nonarthritic animals, while animals treated with triptolide and prednisolone exhibited weight gains comparable to the adjuvant arthritis control animals. Potentially useful for the treatment of autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease, diabetes mellitus type I, multiple sclerosis, psoriasis and lupus, as well as transplant rejection and graft-versus-host disease. Other compounds within this series of triptolide derivatives include the following:



Compound	R1	R2	Formula
271615	OH	H	C ₂₀ H ₂₇ ClO ₆
271616	-O-		C ₂₀ H ₂₅ ClO ₆

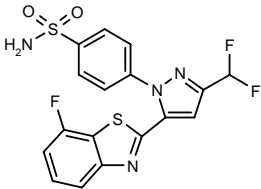
SOURCE – Hoechst Marion Roussel.

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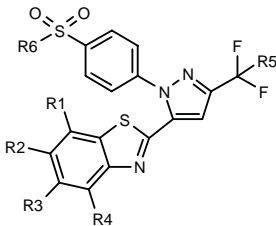
271706

4-[3-(Difluoromethyl)-5-(7-fluorobenzothiazol-2-yl)pyrazol-1-yl]benzenesulfonamide



C17 H11 F3 N4 O2 S2; Mol wt: 424.4259

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2) with an IC₅₀ value of 0.012 μM versus an IC₅₀ of > 100 μM for COX-1. It was active in the adjuvant-induced arthritis model in rats at a dose of 1 mg/kg/day p.o. for 17 consecutive days. Within this series of pyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
271707	H	F	H	H	F	Me	C ₁₈ H ₁₁ F ₄ N ₃ O ₂ S ₂
271708	H	H	F	H	F	Me	C ₁₈ H ₁₁ F ₄ N ₃ O ₂ S ₂
271709	H	H	H	F	F	Me	C ₁₈ H ₁₁ F ₄ N ₃ O ₂ S ₂
271710	F	H	H	H	F	NH2	C ₁₇ H ₁₀ F ₄ N ₄ O ₂ S ₂
271711	H	F	H	H	H	Me	C ₁₈ H ₁₂ F ₃ N ₃ O ₂ S ₂
271712	H	F	H	H	H	NH2	C ₁₇ H ₁₁ F ₃ N ₄ O ₂ S ₂
271713	H	Me	H	H	H	Me	C ₁₉ H ₁₅ F ₂ N ₃ O ₂ S ₂
271714	F	H	H	H	H	Me	C ₁₈ H ₁₂ F ₃ N ₃ O ₂ S ₂
271715	H	Me	H	H	CF3	NH2	C ₁₉ H ₁₃ F ₅ N ₄ O ₂ S ₂

SOURCE – Grelan.

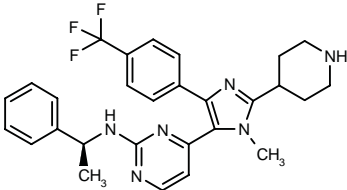
REFERENCES

1. Aotsuka, T. et al. (Grelan Pharmaceutical Co., Ltd.) *Pyrazole derivs. and COX inhibitors containing them.* WO 9846594.

271731

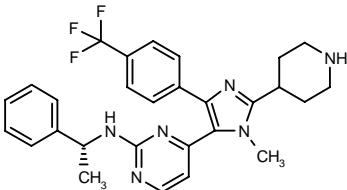
N-[4-[1-Methyl-2-(4-piperidiny)-4-[4-(trifluoromethyl)-phenyl]-1 H-imidazol-5-yl]pyrimidin-2-yl]-N-[1 (S)-phenylethyl]amine

4-[1-Methyl-2-(4-piperidiny)-4-[4-(trifluoromethyl)phenyl]-1 H-imidazol-5-yl]-N-[1 (S)-1-phenylethyl]pyrimidin-2-amine



C28 H29 F3 N6; Mol wt: 506.5731

ACTION – Agent for the treatment of cytokine-mediated diseases such as rheumatoid arthritis and other inflammatory disorders, reported to inhibit the production or activity of IL-1β, tumor necrosis factor (TNF-α), IL-6 and PGE₂. Another representative compound within this series of specifically claimed substituted imidazoles is:



271732: C28 H29 F3 N6

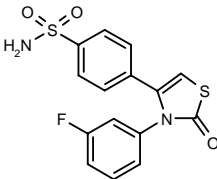
SOURCE – Merck & Co.

REFERENCES

1. Liverton, N.J. et al. (Merck & Co., Inc.) *Substd. imidazoles having cytokine inhibitory activity.* US 5859041.

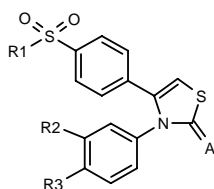
271733

4-[3-(3-Fluorophenyl)-2-oxo-2,3-dihydrothiazol-4-yl]-benzenesulfonamide



C15 H11 F N2 O3 S2; Mol wt: 350.3929

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.24 μM against purified enzyme from sheep placenta vs. 335 μM against purified COX-1 from sheep seminal vesicles; ratio COX-1/COX-2 = 1367). Antiinflammatory activity was demonstrated in the carrageenan-induced edema test in rats (ED₅₀ = 2.8 mg/kg p.o.), and analgesic activity was shown in the kaolin-induced arthritis model in rats (ED₅₀ = 1.3 mg/kg p.o.). Within this series of 3,4-diarylthiazolin-2-one derivatives, the following compounds are also included:



Compound	R1	R2	R3	A	Formula
271734	NH ₂	F	H	S	C ₁₅ H ₁₁ FN ₂ O ₂ S ₃
271735	Me	H	Cl	O	C ₁₆ H ₁₂ ClNO ₃ S ₂

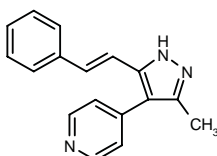
SOURCE – UPSA.

REFERENCES

1. Sartori, E. and Teulon, J.-M. (Laboratoires UPSA) 3,4-Diarylthiazolin-2-one or -2-thione derivs., their methods of preparation and their uses in therapeutics. US 5859036.

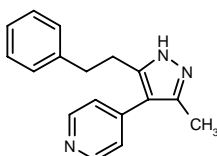
272170

4-[3-Methyl-5-(2-phenylvinyl)-1*H*-pyrazol-4-yl]pyridine



C17 H15 N3; Mol wt: 261.3265

ACTION – An inhibitor of p38 MAP (mitogen-activated protein) kinase, particularly p38- α kinase, as demonstrated *in vitro* in the PHAS-I (phosphorylated heat and acid stable protein-insulin inducible) and epidermal growth factor receptor peptide phosphorylation assays (IC_{50} = 8.7 and 0.66 μ M, respectively). In addition, it inhibited the production of tumor necrosis factor (TNF- α) in lipopolysaccharide (LPS)-stimulated human histiocytic lymphoma U937 cells (IC_{50} = 0.6 μ M). Potentially useful for the treatment or prevention of a broad range of p38-mediated disorders such as rheumatoid arthritis, osteoarthritis, bone resorption, atherosclerosis, graft-versus-host reaction, gout, psoriasis, asthma, cardiac and renal reperfusion injury, thrombotic disorders, glomerulonephritis, inflammatory bowel disease and cachexia. A representative compound from a series of pyrazole derivatives, wherein the following is also included:



272171: C17 H17 N3

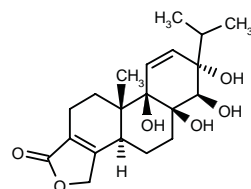
SOURCE – Searle.

REFERENCES

1. Hanson, G.J. and Liao, S. (G.D. Searle & Co.) Pyrazole derivs. as p38 kinase inhibitors. WO 9852941.

272173

(3*bS*,5*aR*,6*R*,7*S*,9*aR*,9*bS*)-5*a*,6,7,9*a*-Tetrahydroxy-7-isopropyl-9*b*-methyl-1,3,3*b*,4,5,5*a*,6,7,9*a*,9*b*,10,11-dodecahydrophenanthro[1,2-*c*]furan-1-one



C20 H28 O6; Mol wt: 364.4352

ACTION – Immunosuppressant and antiinflammatory agent, a derivative of triptolide found to inhibit IL-2 production in Jurkat E6-1 cells with comparable potency to triptolide (IC_{50} = 14 ng/ml vs. 1-3 ng/ml for triptolide), while exhibiting lower cytotoxicity (IC_{50} = 90 ng/ml vs. 5 ng/ml for triptolide). *In vivo*, compound was tested in a rat model of adjuvant-induced arthritis, where it gave 83% inhibition at 2 mg/kg/day i.p. compared to values of 85% for triptolide at 0.4 mg/kg/day i.p., 100% for ciclosporin at 10 mg/kg/day i.p. and 100% for prednisolone at 15 mg/kg/day i.p.

SOURCE – Hoechst Marion Roussel.

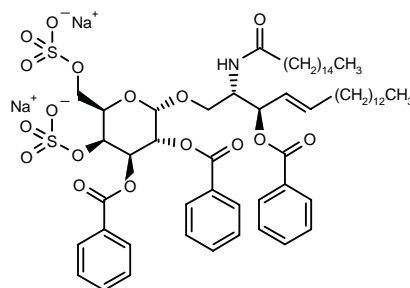
REFERENCES

1. Jung, M.J. et al. (Hoechst Marion Roussel, Inc.) Novel triptolide derivs. useful in the treatment of autoimmune diseases. WO 9852933.

BMS-184000*

232498

2,3-Di-*O*-benzoyl-1-*O*-[3(*R*)-benzoyloxy-2(*S*)-(hexadecanamido)-4(*E*)-octadecenyl]-4,6-di-*O*-sulfo- α -D-galactopyranose disodium salt



C61 H87 N Na2 O17 S2; Mol wt: 1216.4600

ACTION – An inhibitor of selectin-dependent cell adhesion, a synthetic analogue of sulfatide that blocks P-selectin-dependent adhesion of platelets to HL-60 cells and the adhesion of cells to P-selectin-Ig complex. Compound also inhibits the adhesion of HL-60 cells to E-selectin and of LS-180 cells to L-selectin. *In vivo*, it displays antiinflammatory activity in acute inflammation models such as the reverse passive Arthus reaction and murine delayed-type hypersensitivity reaction, but not in chronic inflammation such as collagen-induced arthritis in mice.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Martel, A. et al. (Bristol-Myers Squibb Co.) *Sulfated α -glycolipid derivs. as cell adhesion inhibitors*. EP 671407, JP 96041093, US 5663151.

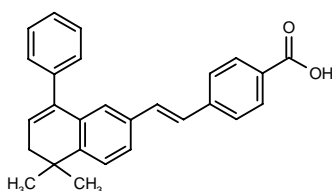
2. Todderud, G. et al. *Suppression of acute inflammation by a novel inhibitor of selectin-dependent cell adhesion*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst W46.

*Identified compound **232498** Drug Data Report 1996, 018(04): 0368.

BMS-453

269779

(E)-4-[2-(5,5-Dimethyl-8-phenyl-5,6-dihydronaphthalen-2-yl)vinyl]benzoic acid



C27 H24 O2; Mol wt: 380.4846

ACTION – Retinoic acid receptor (RAR α , RAR β and RAR γ) antagonist proven to suppress the expression of the matrix metalloproteinases (MMPs) collagenase and stromelysin 1 *in vivo* in a model of collagen-induced arthritis in mice, as well as to delay the onset of clinical signs, reduce the severity of arthritis symptoms and improve joint integrity.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Shannon, R.J. et al. (Bristol-Myers Squibb Co.) *Use of subst. (5,6)-dihydronaphthalenyl cpds. having retinoid-like activity to prevent or reduce ischemic injury*. WO 9836746.

2. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Subst. (5,6)-dihydronaphthalenyl cpds. having retinoid-like activity*. CA 2138000, EP 661259, JP 95242591, US 5648385.

3. Tramposch, K.M. et al. (Bristol-Myers Squibb Co.) *Retinoid antagonists and uses thereof*. WO 9846228.

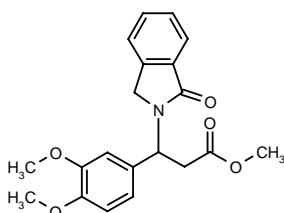
4. Hei, Y.-J. et al. *Mouse collagen-induced arthritis (CIA) induces over-expression of matrix metalloproteinases (MMPs): Suppression by a retinoic acid receptor antagonist*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst P7.

5. Yang, L.-M. et al. *Inhibition of breast cell growth by retinoids does not require activation of RARs*. Proc Amer Assoc Cancer Res 1997, 38 Abst 3042.

CC-3052

269953

3-(3,4-Dimethoxyphenyl)-3-(1-oxo-1,3-dihydroisoindol-2-yl)propionic acid methyl ester



C20 H21 N O5; Mol wt: 355.3879

ACTION – Water-soluble thalidomide analogue proven to inhibit lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF- α) production in whole blood with an IC₅₀ of 1.22 μ M; in addition to its significantly improved potency compared to thalidomide (IC₅₀ approx. 200 μ M), it showed increased stability in human plasma and appears to be nontoxic, nonmutagenic and nonteratogenic. Inhibition of TNF- α production was closely correlated with inhibition of phosphodiesterase type 4 (PDE4; IC₅₀ = 3 μ M). Excellent candidate for further investigation and clinical evaluation as a therapeutic agent for TNF- α -mediated pathologies such as rheumatoid arthritis.

SOURCE – Celgene.

REFERENCES

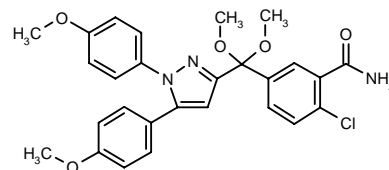
1. Guckian, M. et al. *The effect of thalomid analogue CC-3052 on apoptosis of lymphocytes and neutrophils in HIV*. Immunology 1997, 92(Suppl. 1): Abst 1.8.

2. Marriott, J.B. et al. *CC-3052: A water-soluble analog of thalidomide and potent inhibitor of activation-induced TNF- α production*. J Immunol 1998, 161(8): 4236.

ER-34122*

237949

5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzamide



C27 H26 Cl N3 O5; Mol wt: 507.9714

ACTION – Antiinflammatory agent, a potent dual 5-lipoxygenase (5-LO) and cyclooxygenase (COX) inhibitor with some activity against thromboxane synthase (IC₅₀ = 0.15, 0.06 and 4.2 μ M, respectively). Compound was as potent as indomethacin against COX and as potent as zileuton against 5-LO. ER-34122 inhibited the production of LTB₄ in human polymorphonuclear cells and monocytes (IC₅₀ = 0.25 and 0.39 μ M, respectively) and of PGE₂ in human synovial cells and monocytes (IC₅₀ = 0.34 and 1.49 μ M, respectively). Following oral administration, it inhibited *ex vivo* LTB₄ synthesis (ED₅₀ = 0.078 mg/kg) and TxB₂ production (ED₅₀ = 0.28 mg/kg) in murine whole blood. In rats, it exhibited antiinflammatory activity in two models of acute inflammation: in the carrageenan-induced edema model it decreased paw edema at doses of 3-100 mg/kg p.o., with a potency lower than indomethacin, and in the arachidonic acid-induced ear edema model it inhibited both edema formation and polymorphonuclear infiltration (ED₅₀ = 1.6 and 1.3 mg/kg p.o., respectively), as well as eicosanoid (LTB₄, LTC₄ and PGE₂) generation, being about 10-20-fold more potent than zileuton (indomethacin was inactive).

SOURCE – Eisai.

REFERENCES

1. Numata, H. et al. (Eisai Co., Ltd.) *Pyrazole derivs. exhibiting anti-inflammatory and analgesic effects*. JP 98509140, WO 9614302.

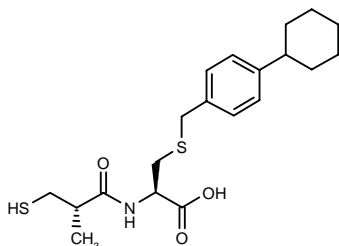
2. Horioe, T. et al. *ER-34122, a novel dual 5-lipoxygenase/cyclooxygenase inhibitor with potent anti-inflammatory activity in an arachidonic acid-induced ear inflammation*. Inflamm Res 1998, 47(10): 375.

*Identified compound **237949** Drug Data Report 1996, 018(09): 0823.

SA-9499*

264786

S-(4-Cyclohexylbenzyl)-*N*-[2(*S*)-methyl-3-sulfanylpropionyl]-L-cysteine



C20 H29 N O3 S2; Mol wt: 395.5851

ACTION – Potent and selective LTA₄ hydrolase inhibitor (IC₅₀ = 79 nM) with low inhibitory activity against angiotensin-converting enzyme (ACE; IC₅₀ = 4000 nM). Potentially useful for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.

SOURCE – Santen.

REFERENCES

1. Horiuchi, M. et al. (Santen Pharmaceutical Co., Ltd.) *Novel sulfur-containing amino acid derivs.* JP 98130225, WO 9809943.

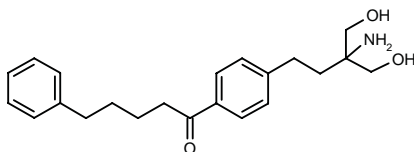
2. Enomoto, H. et al. *The investigation of leukotriene A4 hydrolase inhibitors. Synthesis and inhibitory activities of cysteine derivatives of SA6541 as a lead compound.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-25.

*Identified compound **264786** (see **263796**) Drug Data Report 1998, 020(07): 0611.

IMMUNOMODULATING AGENTS

271589

1-[4-[3-Amino-4-hydroxy-3-(hydroxymethyl)butyl]phenyl]-5-phenyl-1-pentanone



C22 H29 N O3; Mol wt: 355.4751

ACTION – Immunosuppressive agent for the treatment or prevention of organ or bone marrow transplant rejection, rheumatoid arthritis, autoimmune and allergic diseases.

SOURCE – Yoshitomi.

REFERENCES

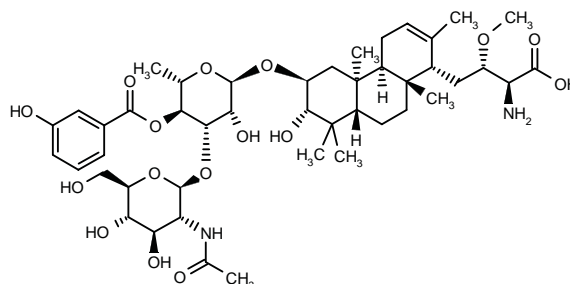
1. Adachi, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *2-Aminopropane-1,3-diol cpds., medicinal use thereof, and intermediates in synthesizing the same.* WO 9845249.

BRASILICARDIN A

271245

[2*S*,3*S*,4(1*S*,4*aS*,4*bS*,6*S*,7*S*,8*aS*,10*aS*)]-4-[6-[3-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-6-deoxy-4-*O*-(3-hydroxybenzoyl)-α-L-mannopyranosyloxy]-7-hydroxy-2,4*b*,8,8,10*a*-pentamethyl-1,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthren-1-yl]-2-amino-3-methoxybutyric acid

0406TP-1



C45 H68 N2 O16; Mol wt: 893.0302

Colorless amorphous solid, m.p. 270-3 °C, [α]_D³⁰ +15.0° (c 0.50, MeOH).

ACTION – Macrolide immunosuppressant isolated from *Nocardia brasiliensis* IFM 0406, with immunosuppressive activity (IC₅₀ = 0.07 µg/ml in the mouse mixed lymphocyte assay) comparable to that of ciclosporin and ascomycin, but suggested to have a different mechanism of action. Cytotoxic activity was observed against murine leukemia L1210 (IC₅₀ = 1.2 µg/ml), human epidermal carcinoma KB (IC₅₀ = 1.3 µg/ml) and doxorubicin-resistant murine leukemia P388/ADM cells (IC₅₀ = 0.22 µg/ml), and it also exhibited antifungal activity against *Paecilomyces variotti* (MIC = 25 µg/ml). In a human tumor screen, it exhibited activity different from that of known antitumor compounds, giving a mean GI₅₀ value of about 0.43 µM. Brasilicardin A is reportedly the first example of an *anti/syn/anti*-perhydrophenanthrene skeleton with a rhamnose, an *N*-acetylglucosamine and an amino acid moiety.

SOURCE – Higeta Shoyu.

REFERENCES

1. Komaki, H. et al. (Higeta Shoyu Co., Ltd.) *Novel terpenoid cpd. 0406TP1.* EP 855402.

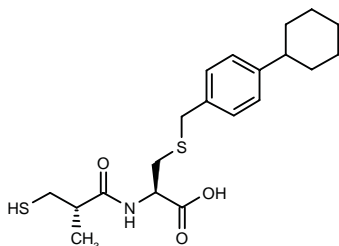
2. Komaki, H. et al. *Brasilicardin A, a new terpenoid antibiotic from pathogenic Nocardia brasiliensis: Fermentation, isolation and biological activity.* J Antibiot 1999, 52(1): 13.

3. Shigemori, H. et al. *Brasilicardin A. A novel tricyclic metabolite with potent immunosuppressive activity from actinomycete Nocardia brasiliensis.* J Org Chem 1998, 63(20): 6900.

SA-9499*

264786

S-(4-Cyclohexylbenzyl)-*N*-[2(*S*)-methyl-3-sulfanylpropionyl]-L-cysteine



C20 H29 N O3 S2; Mol wt: 395.5851

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SOURCE – Santen.

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1. Horiuchi, M. et al. (Santen Pharmaceutical Co., Ltd.) *Novel sulfur-containing amino acid derivs.* JP 98130225, WO 9809943.

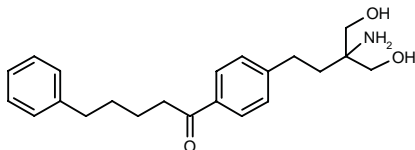
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*Identified compound **264786** (see **263796**) Drug Data Report 1998, 020(07): 0611.

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SOURCE – Yoshitomi.

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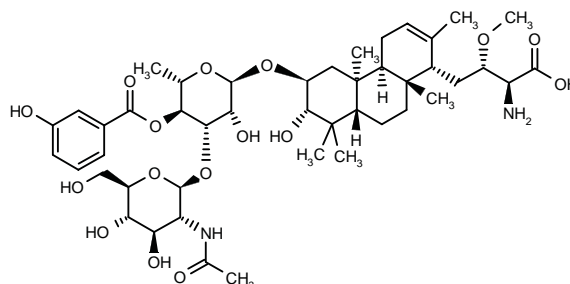
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BRASILICARDIN A

271245

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0406TP-1



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SOURCE – Higeta Shoyu.

REFERENCES

1. Komaki, H. et al. (Higeta Shoyu Co., Ltd.) *Novel terpenoid cpd. 0406TP1.* EP 855402.

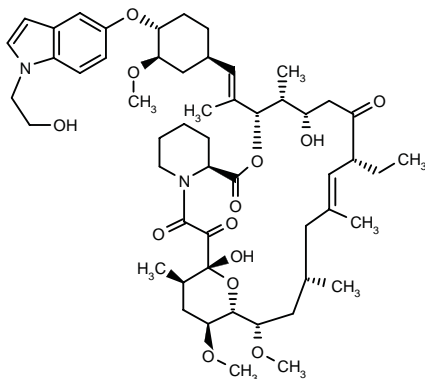
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3. Shigemori, H. et al. *Brasilicardin A. A novel tricyclic metabolite with potent immunosuppressive activity from actinomycete Nocardia brasiliensis.* J Org Chem 1998, 63(20): 6900.

L-732531

270700

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14-dihydroxy-12-[2-[4-[1-(2-hydroxyethyl)-1*H*-indol-5-yloxy]-3-methoxycyclohexyl]-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone



C53 H78 N2 O13; Mol wt: 951.2002

ACTION – Immunosuppressant, a semisynthetic analogue of ascomycin (and tacrolimus) with a mechanism of action similar to tacrolimus (FK-506) but an improved therapeutic index and 10-fold lower affinity for FKBP12. *In vitro*, compound was equipotent to tacrolimus in inhibiting calcineurin phosphatase activity (IC_{50} = 0.13 and 0.12 nM, respectively, in activated Jurkat cells) and in inhibiting human lymphocyte proliferation (IC_{50} = 0.5-1.2 and 0.4-1.6 nM, respectively, in concanavalin A-stimulated cells) and IL-2 promoter activity (IC_{50} = 0.024 and 0.012 nM, respectively, in activated Jurkat cells). In murine models of thyroid and skin transplants, compound was slightly but significantly better than FK-506 in prolonging the survival of allografts. Compound was generally better tolerated than tacrolimus, showing 2-3-fold lower nephrotoxicity, neurotoxicity and gastrointestinal toxicity.

SOURCE – Merck & Co.

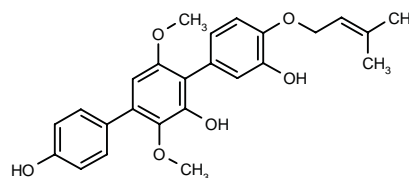
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2. Brands, K.M.J. et al. *Mild aryl ether formation in the semisynthesis of the novel macrolide immunosuppressant L-732,531*. J Org Chem 1998, 63(19): 6721.
3. Dumont, F.J. et al. *A tacrolimus-related immunosuppressant with reduced toxicity*. Transplantation 1998, 65(1): 18.
4. Karanam, B.V. et al. *Disposition of L-732,521, a potent immunosuppressant, in rats and baboons*. Drug Metab Dispos 1998, 26(10): 949.
5. Peterson, L.B. et al. *A tacrolimus-related immunosuppressant with biochemical properties distinct from those of tacrolimus*. Transplantation 1998, 65(1): 10.
6. Salowe, S.P. and Hermes, J.D. *Competitive and slow-binding inhibition of calcineurin by drug - Immunophilin complexes*. Arch Biochem Biophys 1998, 355(2): 165.

TERPRENIN*

257713

3',6'-Dimethoxy-4-(3-methyl-2-butenyloxy)-*p*-terphenyl-2',3,4''-triol



C25 H26 O6; Mol wt: 422.4744

Colorless crystals, m.p. 155.5-6.0 °C.

ACTION – Immunosuppressant isolated from the fermentation broth of *Aspergillus candidus* RF-5672 (FERM BP-5882), with strong immunosuppressive activity *in vitro* against concanavalin A- and lipopolysaccharide-stimulated murine spleen lymphocyte proliferation (IC_{50} = 1.2 and 4.5 ng/ml, respectively), and also reported to potently suppress IgE antibody production without toxicity. It is devoid of antimicrobial activity against bacteria or fungi.

SOURCE – Shionogi.

REFERENCES

1. Kamigauchi, T. and Suzuki, R. (Shionogi & Co. Ltd.) *Novel terphenyl cpds. and medicines containing the same*. EP 895981, WO 9739999.
2. Kamigauchi, T. et al. *Terprenins, novel immunosuppressants produced by Aspergillus candidus*. J Antibiot 1998, 51(4): 445.
3. Yonezawa, S. et al. *Total synthesis of terprenin, a novel immunosuppressive p-terphenyl derivative*. J Org Chem 1998, 63(17): 5831.

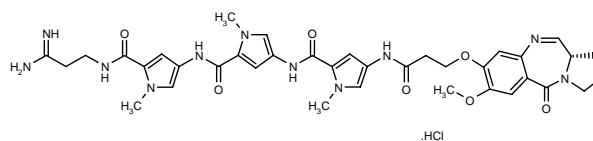
*Identified compound **257713** Drug Data Report 1998, 020(05): 0448.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

270082

3-[4-[4-[4-[3-(7-Methoxy-5-oxo-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-8-yloxy)propionamido]-1-methylpyrrole-2-carboxamido]-1-methylpyrrole-2-carboxamido]-1-methylpyrrole-2-carboxamido]propionamide hydrochloride

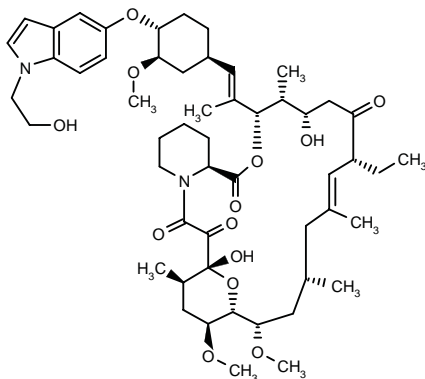


C37 H43 N11 O7 . HCl; Mol wt: 790.2776

L-732531

270700

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14-dihydroxy-12-[2-[4-[1-(2-hydroxyethyl)-1*H*-indol-5-yloxy]-3-methoxycyclohexyl]-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone



C53 H78 N2 O13; Mol wt: 951.2002

ACTION – Immunosuppressant, a semisynthetic analogue of ascomycin (and tacrolimus) with a mechanism of action similar to tacrolimus (FK-506) but an improved therapeutic index and 10-fold lower affinity for FKBP12. *In vitro*, compound was equipotent to tacrolimus in inhibiting calcineurin phosphatase activity (IC_{50} = 0.13 and 0.12 nM, respectively, in activated Jurkat cells) and in inhibiting human lymphocyte proliferation (IC_{50} = 0.5-1.2 and 0.4-1.6 nM, respectively, in concanavalin A-stimulated cells) and IL-2 promoter activity (IC_{50} = 0.024 and 0.012 nM, respectively, in activated Jurkat cells). In murine models of thyroid and skin transplants, compound was slightly but significantly better than FK-506 in prolonging the survival of allografts. Compound was generally better tolerated than tacrolimus, showing 2-3-fold lower nephrotoxicity, neurotoxicity and gastrointestinal toxicity.

SOURCE – Merck & Co.

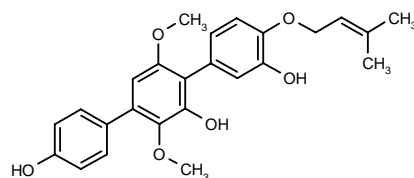
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1. Sinclair, P.J. et al. (Merck & Co., Inc.) *O*-Heteroaryl, *O*-alkylheteroaryl, *O*-alkenylheteroaryl and *O*-alkynylheteroaryl macrolides. EP 532088, JP 94116274, US 5252732, WO 9305058.
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5. Peterson, L.B. et al. *A tacrolimus-related immunosuppressant with biochemical properties distinct from those of tacrolimus*. Transplantation 1998, 65(1): 10.
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SOURCE – Shionogi.

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1. Kamigauchi, T. and Suzuki, R. (Shionogi & Co. Ltd.) *Novel terphenyl cpds. and medicines containing the same*. EP 895981, WO 9739999.
2. Kamigauchi, T. et al. *Terprenins, novel immunosuppressants produced by Aspergillus candidus*. J Antibiot 1998, 51(4): 445.
3. Yonezawa, S. et al. *Total synthesis of terprenin, a novel immunosuppressive p-terphenyl derivative*. J Org Chem 1998, 63(17): 5831.

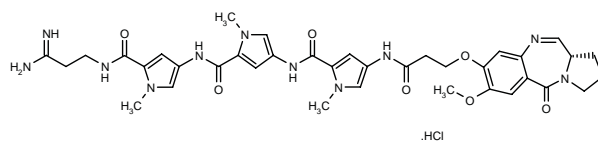
*Identified compound **257713** Drug Data Report 1998, 020(05): 0448.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

270082

3-[4-[4-[4-[3-(7-Methoxy-5-oxo-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-8-yloxy)propionamido]-1-methylpyrrole-2-carboxamido]-1-methylpyrrole-2-carboxamido]-1-methylpyrrole-2-carboxamido]propionamide hydrochloride



C37 H43 N11 O7 . HCl; Mol wt: 790.2776

ACTION – Antineoplastic agent, a hybrid of the natural antitumor agent distamycin and a pyrrolo[2,1-c][1,4]-benzodiazepine with antiproliferative activity in human leukemia K562 cells ($IC_{50} = 0.2 \mu M$) significantly greater than that of its components given alone and in combination. It was also much more active than the components in binding to DNA.

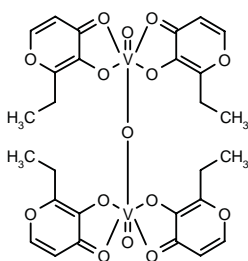
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Baraldi, P.G. et al. *Design, synthesis and biological activity of a pyrrolo[2,1-c][1,4]-benzodiazepine (PBD)-distamycin hybrid*. *Bioorg Med Chem Lett* 1998, 8(21): 3019.

271045

(μ -Oxido)bis[2-ethyl-4-oxopyran-3-olato(1-)- O^3, O^4]-oxovanadium]



C28 H28 O15 V2; Mol wt: 706.3982

ACTION – Vanadium complex with antiproliferative, antimetastatic and antitumor activity, reported to possess enhanced efficacy and stability compared to known compounds. Also claimed for use in the treatment of bone destruction, arthritis, psoriasis, multiple sclerosis, diabetes, ocular diseases, diabetic complications, hypertension, obesity, lupus erythematosus, bacterial infections, periodontal disease, surgical adhesions and inflammatory bowel disease (IBD).

SOURCE – Angiotech.

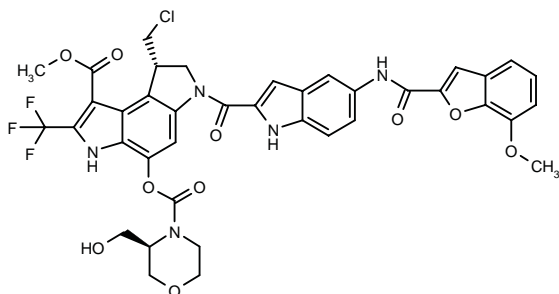
REFERENCES

1. Zhang, Z. et al. (Angiotech Pharmaceuticals, Inc.) *Vanadium complexes and derivs. thereof and methods related thereto*. WO 9849173.

AT-5015

270150

8(S)-(Chloromethyl)-4-[3(R)-(hydroxymethyl)morpholin-4-yl]-6-[5-(7-methoxybenzofuran-2-ylcarboxamido)-1H-indol-2-ylcarbonyl]-2-(trifluoromethyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-1-carboxylic acid methyl ester



C39 H33 Cl F3 N5 O10; Mol wt: 824.1617

ACTION – Antineoplastic agent, a cyclopropapyrroloindole (CPI) prodrug with *in vivo* antitumor activity superior to carzelesin. Compound is hydrolyzed *in vivo* and converted to the active DNA-alkylating agent.

SOURCES – Kyorin; Sagami.

REFERENCES

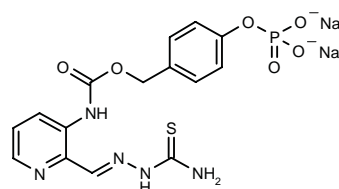
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2. Ebisu, H. and Oomori, Y. *Antitumor activity of AT-5015, a novel cyclopropapyrroloindole compound, against human tumor xenografts*. *Jpn J Cancer Res* 1998, 89(Suppl.): Abst 2240.
3. Fukuda, Y. et al. *Novel prodrugs of cyclopropapyrroloindole derivatives*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-12.
4. Oomori, Y. et al. *Antitumor activity of AT-5015, a novel cyclopropapyrroloindole compound, in murine tumor models*. *Jpn J Cancer Res* 1998, 89(Suppl.): Abst 2239.

ANTIMETABOLITES

270651

265007 (as free acid)⁺

N-[2-(Thiosemicarbazonomethyl)pyridin-3-yl]carbamic acid 4-(phosphonoxy)benzyl ester sodium salt



C15 H14 N5 Na2 O6 P S; Mol wt: 469.3246

ACTION – Antineoplastic agent, a water-soluble phosphate prodrug of the ribonucleotide reductase inhibitor 3-AP⁺⁺ that retains the *in vivo* efficacy of the parent compound but exhibits improved oral bioavailability (91% in dogs). In mice bearing murine lung carcinoma M-109, compound at a dose of 10 mg/kg i.p. reduced tumor growth by 46-57%, being slightly more effective than equimolar doses of 3-AP; however, the therapeutic index was not improved. Chemical modifications are thus being pursued to improve the biological profile of the compound.

SOURCE – Vion.

REFERENCES

1. Li, J. et al. (Vion Pharmaceuticals, Inc.) *Prodrug forms of ribonucleotide reductase inhibitors 3-AP and 3-AMP*. US 5767134, WO 9851669.
2. Li, J. et al. *Synthesis and biological evaluation of a water soluble phosphate prodrug of 3-aminopyridine-3-carboxaldehyde thiosemicarbazone (3-AP)*. *Bioorg Med Chem Lett* 1998, 8(22): 3159.

⁺Drug Data Report 1998, 020(07): 0620.

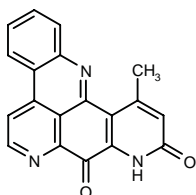
⁺⁺Drug Data Rep 1998, 20(6): 535.

ANTIBIOTICS AND ALKALOIDS

IB-96213

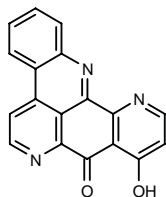
271048

12-Methyl-9,10-dihydro-8*H*-benzo[*b*]pyrido[4,3,2-*de*][1,7]-phenanthroline-8,10-dione



C₁₉ H₁₁ N₃ O₂; Mol wt: 313.3149

ACTION – Antineoplastic alkaloid particularly active against cell lines derived from human solid tumors such as human lung carcinoma A-549 (IC₅₀ = 0.003 μM), human colon carcinoma HT-29 (IC₅₀ = 3.18 μM) and human melanoma MEL-28 (IC₅₀ = 0.003 μM), as well as murine leukemia P388 (IC₅₀ = 0.32 μM). Another preferred compound within this series of pyrido[2,3,4-*k*]acridine derivatives is:



IB-98205 [271049]: C₁₈ H₉ N₃ O₂

SOURCE – Universidad Complutense de Madrid, Madrid (ES).

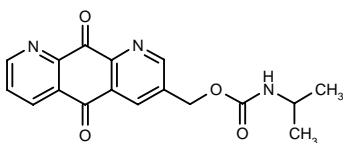
REFERENCES

1. Fernandez Puentes, J.L. et al. (Universidad Complutense de Madrid) *Cytotoxic cpds.: Derivs. of the pyrido[2,3,4-*k*]acridine ring system*. WO 9849165.

DNA-INTERCALATING DRUGS

270081

N-Isopropylcarbamic acid 5,10-dioxo-5,10-dihydropyrido-[3,2-*g*]quinolin-3-ylmethyl ester



C₁₇ H₁₅ N₃ O₄; Mol wt: 325.3225

ACTION – Antineoplastic agent, an intercalating agent from a series of 1,8-diazaanthraquinones with *in vitro* cytotoxic activity against human tumor cell lines such as lung HOP62 (IC₅₀ = 6 nM), ovarian SK-OV-3 (IC₅₀ = 20 nM), colon HCT-15 (IC₅₀ = 20 nM) and CNS SF295 cells (IC₅₀ = 100 nM); its activity was comparable or superior to that of the standard doxorubicin against HOP62, SK-OV-3 and HCT-15 cells.

SOURCES – Chungbuk National University, Cheongju, (KR); Kun-Kuk University, Chungju (KR).

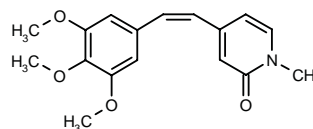
REFERENCES

1. Lee, H. et al. *Synthesis and in vitro cytotoxicity of 3-substituted-1,8-diazaanthraquinones produced by Lewis-acid catalyzed hetero Diels-Alder reaction*. Bioorg Med Chem Lett 1998, 8(21): 2991.

ANTIMITOTIC DRUGS

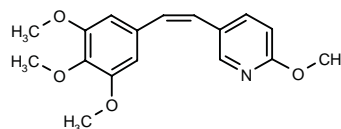
270693

(*Z*)-1-Methyl-4-[2-(3,4,5-trimethoxyphenyl)vinyl]-2(1*H*)-pyridinone



C₁₇ H₁₉ N O₄; Mol wt: 301.3401

ACTION – Antimitotic agent derived from combretastatin A-4 (CA-4), with strong antitubulin activity (IC₅₀ = 2 μM for inhibition of bovine brain tubulin polymerization) and cytotoxicity against murine colon adenocarcinoma colon 26 cells (IC₅₀ = 19.2 nM). It is equipotent but more soluble than CA-4. Currently being evaluated in *in vivo* studies. Another related B-ring modified CA-4 analogue is:



270694: C₁₇ H₁₉ N O₄

SOURCE – Ajinomoto.

REFERENCES

1. Hatanaka, T. et al. *Novel B-ring modified combretastatin analogues: Synthesis and antineoplastic activity*. Bioorg Med Chem Lett 1998, 8(23): 3371.

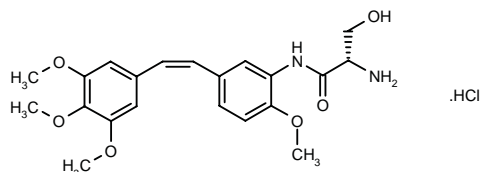
AC-7700*

262298

244066** (as free base)

N-[2-Methoxy-5-[2(*Z*)-(3,4,5-trimethoxyphenyl)-vinyl]phenyl]-L-serinamide hydrochloride

2(*S*)-Amino-3-hydroxy-*N*-[2-methoxy-5-[(*Z*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]propanamide hydrochloride



C21 H26 N2 O6 . HCl; Mol wt: 438.9053

ACTION – Antineoplastic agent, a combretastatin A-4 (CA-4) derivative and serine prodrug of AC-7739 that acts by inhibiting tubulin polymerization. It displays cytotoxic effects comparable to CA-4 against murine and human tumor cell lines. *In vivo*, compound at the maximum tolerated dose (40 mg/kg) markedly suppressed the growth of colon 26 (%TC = 23 vs. 36 for cisplatin) and, in contrast to cisplatin, retained its activity against advanced tumors (%T/C = 24 vs. 66 for cisplatin). It was also curative in mice bearing advanced colon 38 and Meth A tumors, producing cure in 2 of 5 mice and prolonging survival (ILS > 87%) in colon 38-bearing animals.

SOURCE – Ajinomoto.

REFERENCES

- Hatanaka, T. et al. (Ajinomoto Co., Inc.) *Stilbene derivs. and pharmaceutical compsns. containing them*. CA 2171275, EP 731085, JP 96301831, US 5674906.
- Hatanaka, T. et al. *Synthesis and antitumor activity of AC-7700; cis-stilbene type antitumor agent effective against solid tumor model*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-14.
- Hori, K. et al. *Antitumor activity of a novel combretastatin A-4 derivative, AC7700: The effect due to irreversible obstruction of tumor tissue blood flow*. Jpn J Cancer Res 1998, 89(Suppl.): Abst 2253.
- Morinaga, Y. et al. *AC-7700, a novel CS A-4 derivative, exerts potent antitumor activity on solid tumors at advanced growth stage*. Jpn J Cancer Res 1998, 89(Suppl.): Abst 568.
- Nihei, Y. et al. *A novel combretastatin A-4 (CSA-4) derivative, AC-7700 exerts antitumor activity through indirect action on tumor cells*. Jpn J Cancer Res 1998, 89(Suppl.): Abst 2252.
- Nihei, Y. et al. *Anti-vascular effects of AC-7700 on solid tumors; Comparison with other tubulin binding agents*. Proc Amer Assoc Cancer Res 1998, 39: Abst 324.
- Nihel, Y. et al. *A novel combretastatin-A4 derivative AC-7700 shows marked antitumor activity against advanced solid tumors*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1143.
- Ohsumi, K. et al. *Syntheses and antitumor activity of cis-restricted combretastatins: 5-Membered heterocyclic analogues*. Bioorg Med Chem Lett 1998, 8(22): 3153.
- Suga, Y. et al. *Synergistic effect of the novel anticancer drug AC-7700 and CDDP against murine tumor colon26 model*. Jpn J Cancer Res 1998, 89(Suppl.): Abst 2254.

*Identified compound **262298** (see **AC-7739**) Drug Data Report 1998, 020(05): 0439.

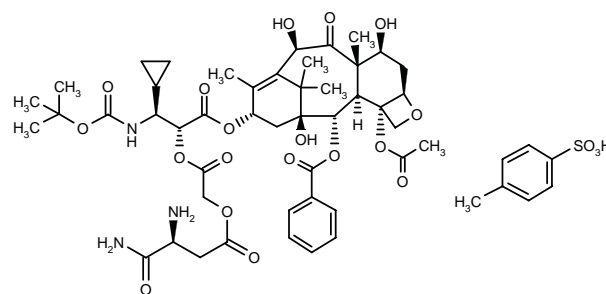
Identified compound **244066 (see **241850**) Drug Data Report 1997, 019(01): 0090.

T-3782*

270156

262774 (as mesylate)

[2a*R*-[2α,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12α,12bα]]-12b-Acetoxy-9-[2(*R*)-[2-[3(*S*)-amino-3-carbamoyl-propionyloxy]acetoxy]-3(*S*)-(tert-butoxycarbonylamino)-3-cyclopropylpropionyloxy]-12-(benzoyloxy)-4,6,11-tri-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methano-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one tosylate



C46 H61 N3 O18 . C7 H8 O3 S; Mol wt: 1116.1940

ACTION – Antineoplastic agent, a water-soluble taxane derivative with excellent *in vivo* antitumor activity against murine B16 melanoma (ILS = 188.3 and 172.4%, respectively, at 12.5 mg/kg/day i.p. and i.v.), showing enhanced efficacy with respect to paclitaxel and docetaxel.

SOURCE – Tanabe.

REFERENCES

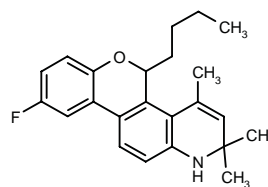
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- Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 98045583.
- Hashiyama, T. et al. *Synthesis of water-soluble taxoid T-3782 and its antitumor activity*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-13.

*Identified compound **262774** (see **261865**) Drug Data Report 1998, 020(06): 0538.

HORMONAL AGENTS

270692

5-Butyl-9-fluoro-2,2,4-trimethyl-2,5-dihydro-1*H*-[1]benzo-pyran[3,4-*f*]quinoline



C23 H26 F N O; Mol wt: 351.4624

ACTION – Nonsteroidal human progesterone receptor (hPR) agonist with high affinity for hPR-A receptors ($K_i = 2.9 \pm 0.3$ nM) and good selectivity over both human androgen and glucocorticoid receptors ($K_i = 1330 \pm 496$ and 533 ± 304 nM, respectively); its agonist activity was demonstrated in a cotransfection assay in CV-1 cells ($EC_{50} = 15 \pm 2$ nM; $77 \pm 7\%$ of progesterone maximal effect). *In vivo*, compound inhibited the estrone-induced increase in uterine wet weight and stimulated lobular alveolar bud formation in ovariectomized rats in the dose range of 0.3-3 mg/kg p.o., exhibiting similar activity to medroxyprogesterone acetate. Potentially useful for the treatment of male and female hormone-responsive diseases including cancer.

SOURCE – Ligand.

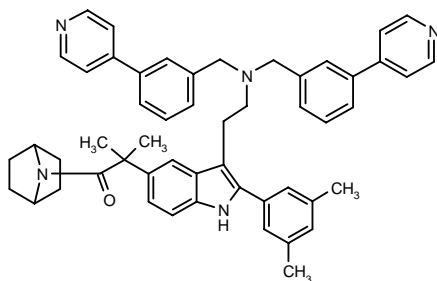
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1. Jones, T.K. et al. (Ligand Pharmaceuticals, Inc.) *Steroid receptor modulator cpds. and methods*. EP 800519, JP 98510840, US 5688808, US 5688810, US 5693646, US 5693647, US 5696127, US 5696130, US 5696133, WO 9619458.

2. Zhi, L. et al. *5-Alkyl 1,2-dihydrochromeno[3,4-f]quinolines: A novel class of nonsteroidal progesterone receptor modulators*. Bioorg Med Chem Lett 1998, 8(23): 3365.

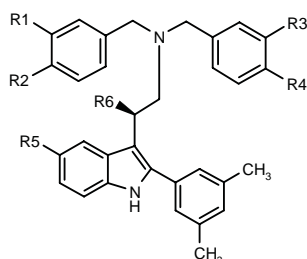
272078

1-(7-Azabicyclo[2.2.1]hept-7-yl)-2-[3-[2-[bis[3-(4-pyridinyl)benzyl]amino]ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-2-methylpropan-1-one



C52 H53 N5 O; Mol wt: 764.0247

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist claimed for the treatment of a variety of sex hormone-related conditions including prostate, uterine and breast cancer, endometriosis, polycystic ovarian disease, benign prostatic hypertrophy, premenstrual syndrome, hirsutism and short stature or growth hormone deficiency, as well as for preventing pregnancy. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1=R3	R2=R4	R5	R6	Formula
272079	3-Pyr	H	CON(i-Pr)2	H	C ₄₉ H ₅₁ N ₅ O
272080	H	4-Pyr-CO	7-azabicyclo[2.2.1]-hept-7-yl-COC(Me)2	Me	C ₅₅ H ₅₈ N ₅ O ₃

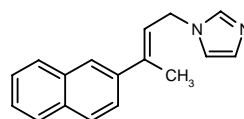
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9855116.

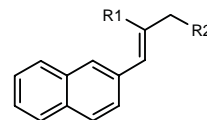
272184

1-[3-(2-Naphthyl)-2(E)-butenyl]-1H-imidazole

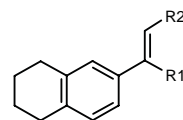


C17 H16 N2; Mol wt: 248.3274

ACTION – Antineoplastic agent that acts by inhibiting steroid C₁₇₋₂₀ lyase ($IC_{50} = 13$ nM in rat testis preparations). Other exemplified compounds include the following:



Compound	R1	R2	Formula
272185	H	1-imidazolyl	C ₁₆ H ₁₄ N ₂
272186	Me	1-imidazolyl	C ₁₇ H ₁₆ N ₂
272187	H	3-Pyr	C ₁₈ H ₁₅ N



Compound	R1	R2	Formula
272188	H	4-Pyr	C ₁₇ H ₁₇ N
272189	Me	1-imidazolyl-CH2	C ₁₇ H ₂₀ N ₂

SOURCE – Takeda.

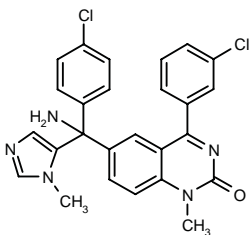
REFERENCES

1. Aono, T. et al. (Takeda Chemical Industries, Ltd.) *Fused ring cpds., process for producing the same and use thereof*. JP 98291981, WO 9837070.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

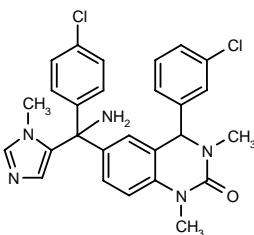
271050

6-[Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)-methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinazolinone



C₂₆ H₂₁ Cl₂ N₅ O; Mol wt: 490.3919

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. Another specifically claimed quinazolinone is:



271051: C₂₇ H₂₅ Cl₂ N₅ O

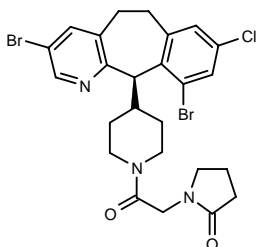
SOURCE – Janssen.

REFERENCES

1. Angibaud, P.R. et al. (Janssen Pharmaceutica NV) *Farnesyltransferase inhibiting quinazolinones*. WO 9849157.

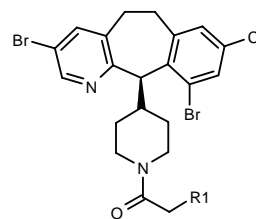
271280

(+)-1-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]pyrrolidin-2-one



C₂₅ H₂₆ Br₂ Cl N₃ O₂; Mol wt: 595.7604

ACTION – Antineoplastic agent, a selective inhibitor of protein farnesyltransferase (IC₅₀ = 0.0040 μM) proven to inhibit Ras processing in COS cells (IC₅₀ = 0.500 μM). Other specifically claimed compounds within this series of benzo[5,6]cycloheptapyridine cyclic ureas and lactams include the following:



Compound	R1	Formula
271281	2-oxo-1-pyrrolidinyl-CH ₂	C ₂₆ H ₂₈ Br ₂ ClN ₃ O ₂
271282	2-oxo-1-pyrrolidinyl-CH ₂ CH ₂	C ₂₇ H ₃₀ Br ₂ ClN ₃ O ₂
271283	2-oxo-1-Pip	C ₂₆ H ₂₈ Br ₂ ClN ₃ O ₂
271284	2-oxo-1-Pip-CH ₂	C ₂₇ H ₃₀ Br ₂ ClN ₃ O ₂
271285	2-oxo-1-Pip-CH ₂ CH ₂	C ₂₈ H ₃₂ Br ₂ ClN ₃ O ₂
271286	1-(2-oxo-1-pyrrolidinyl-CH ₂ CO)-4-Pip	C ₃₂ H ₃₇ Br ₂ ClN ₄ O ₃
271287	1-(2-oxo-1-pyrrolidinyl-CH ₂ CH ₂ CO)-4-Pip	C ₃₃ H ₃₉ Br ₂ ClN ₄ O ₃
271288	1-[2-oxo-1-pyrrolidinyl-(CH ₂) ₃ CO]-4-Pip	C ₃₄ H ₄₁ Br ₂ ClN ₄ O ₃
271289	1-(2-oxo-1-Pip-CH ₂ CO)-4-Pip	C ₃₃ H ₃₉ Br ₂ ClN ₄ O ₃
271290	1-(2-oxo-1-Pip-CH ₂ CH ₂ CO)-4-Pip	C ₃₄ H ₄₁ Br ₂ ClN ₄ O ₃
271291	1-[2-oxo-1-Pip-(CH ₂) ₃ CO]-4-Pip	C ₃₅ H ₄₃ Br ₂ ClN ₄ O ₃

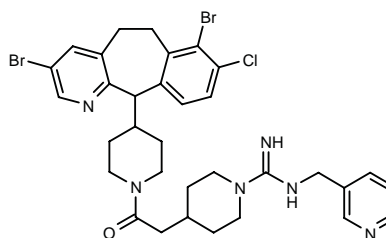
SOURCE – Schering-Plough.

REFERENCES

1. Njoroge, F.G. et al. (Schering Corp.) *Benzo(5,6)cycloheptapyridine cyclic ureas and lactams useful as farnesyl protein transferase inhibitors*. US 5852034, WO 9857963.

271730

4-[2-[4-(3,7-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]-*N*-(3-pyridinylmethyl)piperidine-1-carboxamide



C₃₃ H₃₇ Br₂ Cl N₆ O; Mol wt: 728.9573

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC₅₀ = 0.011 μM) with relatively lower potency against protein geranylgeranyltransferase (IC₅₀ = 7.5 μM). A compound within a series of specifically claimed piperidine derivatives.

SOURCE – Schering-Plough.

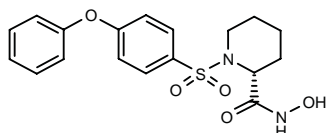
REFERENCES

1. Taveras, A.G. et al. (Schering Corp.) *Cpds. useful for inhibition of farnesyl proteins transferase*. US 5861395.

ANGIOGENESIS INHIBITORS

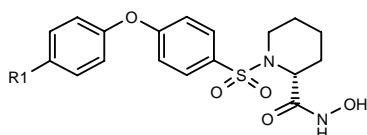
271098

1-(4-Phenoxyphenylsulfonyl)piperidine-2-(*R*)-carbohydroxamic acid



C₁₈ H₂₀ N₂ O₅ S; Mol wt: 376.4310

ACTION – Matrix metalloproteinase (MMP) inhibitor proven to have potent activity against human stromelysin ($K_i = 0.07$ nM), human gelatinase A ($K_i = 0.007$ nM) and human collagenase 3 ($K_i = 0.007$ nM), and also human fibroblast collagenase ($K_i = 6.6$ nM). Potentially useful for the treatment of tumor growth, invasion or metastasis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, stroke, atherosclerosis and the like. Other specifically claimed compounds include the following:



Compound	R1	Formula
271099	Br	C ₁₈ H ₁₉ BrN ₂ O ₅ S
271100	Ph	C ₂₄ H ₂₄ N ₂ O ₅ S

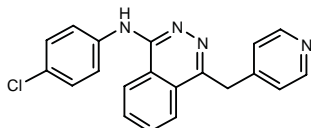
SOURCE – Agouron.

REFERENCES

1. Bender, S.L. (Agouron Pharmaceuticals, Inc.) *Metalloproteinase inhibitors, pharmaceutical compsns. containing them and their pharmaceutical uses*. WO 9850348.

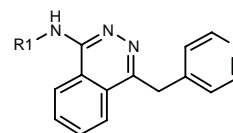
271217

N-(4-Chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine



C₂₀ H₁₅ Cl N₄; Mol wt: 346.8195

ACTION – Antiangiogenic agent that acts by inhibiting vascular endothelial growth factor (VEGF) receptor tyrosine kinase ($IC_{50} = 0.1$ - 0.26 μ M). *In vivo*, compound was shown to inhibit tumor growth in nude mice bearing s.c.-implanted human epidermoid carcinoma A-431 tumors (T/C x 100 = 21, 16 and 9 at 25, 50 and 100 mg/kg/day p.o., respectively). Within this series of phthalazine derivatives, the following are also specifically claimed:



Compound	R1	Formula
271218	4-Me-Ph	C ₂₁ H ₁₈ N ₄
271220	3-Cl-Ph	C ₂₀ H ₁₅ ClN ₄
271221	Ph	C ₂₀ H ₁₆ N ₄
271222	CH ₂ Ph	C ₂₁ H ₁₈ N ₄
271223	4-MeO-Ph	C ₂₁ H ₁₈ N ₄ O
271224	3-(PhCH ₂ O)-Ph	C ₂₇ H ₂₂ N ₄ O
271225	3-MeO-Ph	C ₂₁ H ₁₈ N ₄ O
271226	2-MeO-Ph	C ₂₁ H ₁₈ N ₄ O
271228	4-CF ₃ -Ph	C ₂₁ H ₁₅ F ₃ N ₄
271230	4-F-Ph	C ₂₀ H ₁₅ FN ₄
271231	3-OH-Ph	C ₂₀ H ₁₆ N ₄ O
271233	4-OH-Ph	C ₂₀ H ₁₆ N ₄ O
271234	3-NH ₂ -Ph	C ₂₀ H ₁₇ N ₅
271235	3,4-(Cl) ₂ -Ph	C ₂₀ H ₁₄ Cl ₂ N ₄
271236	4-Br-Ph	C ₂₀ H ₁₅ BrN ₄
271237	3-Cl-4-MeO-Ph	C ₂₁ H ₁₇ ClN ₄ O
271238	4-CN-Ph	C ₂₁ H ₁₅ N ₅
271241	3-Cl-4-F-Ph	C ₂₀ H ₁₄ ClFN ₄
271243	3-Me-Ph	C ₂₁ H ₁₈ N ₄

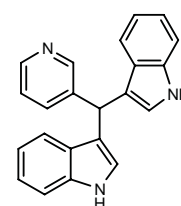
SOURCE – Novartis.

REFERENCES

1. Bold, G. et al. (Novartis AG; Novartis VmbH) *Phthalazines with angiogenesis inhibiting activity*. WO 9835958.

271413

3-[Bis(1*H*-indol-3-yl)methyl]pyridine



C₂₂ H₁₇ N₃; Mol wt: 323.3973

ACTION – Antineoplastic and antimetastatic agent that is believed to act via inhibition of human neutrophil collagenase (MMP-8), proven to significantly inhibit both the number and weight of pulmonary metastases in a murine model of spontaneously metastasizing Lewis lung carcinoma at 200 mg/kg/day i.p., without toxicity.

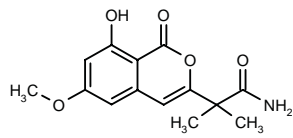
SOURCE – Roche.

REFERENCES

1. Livi, V. et al. (Boehringer Mannheim GmbH) *Bis-indole derivs. having antimetastatic activity, a process for their preparation and pharmaceutical compsns. containing them*. EP 887348, WO 9900381.

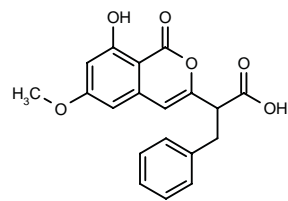
271587

2-(8-Hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl)-2-methylpropionamide



C14 H15 N O5; Mol wt: 277.2745

ACTION – Antiangiogenic agent, as demonstrated by a significant reduction in tumor blood vessels in mice bearing s.c.-implanted S180 tumors at doses of 10 and 30 mg/kg/day p.o. x 5 days. Another compound from this series of isocoumarin derivatives is:



271588: C19 H16 O6

SOURCE – Mercian.

REFERENCES

1. Nakajima, T. et al. (Mercian Corp.) *Isocoumarin derivs. and their pharmaceutical compsns.* JP 98287667.

HUMAN MINDIN

271043

Polypeptide comprising 331 amino acids

ACTION – Integrin ligand; mindin is an F-spondin-like gene that is thought to have proteolytic functions and to play a role in angiogenesis and neural growth and differentiation. The invention includes human mindin polypeptides and polynucleotides, as well as agonists or antagonists thereof, and methods of treating angiogenic diseases, restenosis, Alzheimer’s disease and other neural disorders.

SOURCE – SmithKline Beecham.

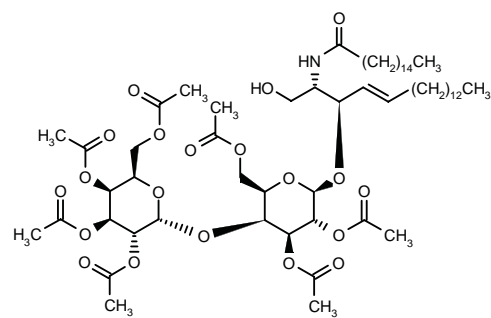
REFERENCES

1. Jonak, Z.L. et al. (SmithKline Beecham Corp.) *Integrin ligand, Human Mindin.* WO 9850073.

OTHER ONCOLYTIC DRUGS

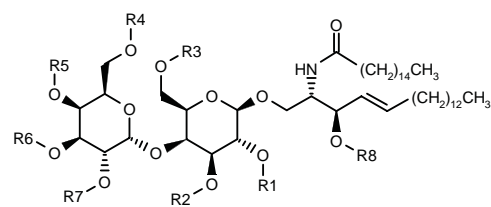
270970

N-[1(*S*)-(Hydroxymethyl)-2(*R*)-[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl)- β -D-galactopyranosyloxy]-3(*E*)-heptadecenyl]hexadecanamide

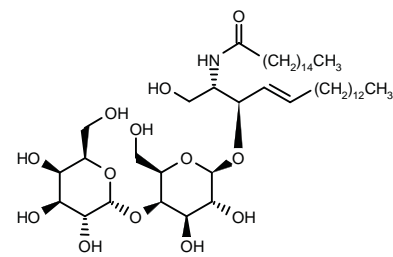


C60 H101 N O20; Mol wt: 1156.4450

ACTION – Digalactosylceramide derivative reported to exert carcinostatic, immunosuppressive and anti-HIV activity and also to be useful for the treatment of Gaucher’s disease. Other exemplified compounds include the following:



Compound	R1=R2=R3=R4=R5=R6=R7	R8	Formula
270972	Ac	COPh	C ₆₇ H ₁₀₆ NO ₂₁
270973	H	H	C ₄₆ H ₈₇ NO ₁₃



270971: C46 H87 N O13

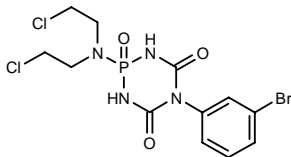
SOURCE – Eisai.

REFERENCES

1. Nakamoto, K. (Eisai Co., Ltd.) *Digalactocylceramide derivs. and their preparation method.* JP 98310596.

270997

2-[Bis(2-chloroethyl)amino]-5-(3-bromophenyl)-1,3,5,2λ⁵-triazaphosphorinane-2,4,6-trione



C12 H14 Br Cl2 N4 O3 P; Mol wt: 444.0516

ACTION – Triazaphosphorine antineoplastic agent with *in vitro* antiproliferative activity against murine leukemia L1210 and K562 cells.

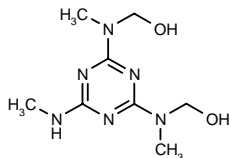
SOURCE – Nankai University, Tianjin (CN).

REFERENCES

1. Lu, S.M. and Chen, R.Y. *Synthesis and biological activity of the derivatives of 2,4,6-trioxo-1,3,5,2-triazaphosphorine*. Chin J Appl Chem 1998, 15(5): 19.

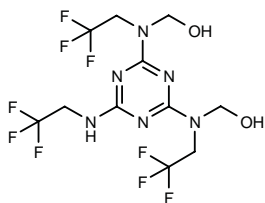
CB-7646**271292**

2,4-Bis[*N*-(hydroxymethyl)-*N*-methylamino]-6-(methylamino)-1,3,5-triazine



C8 H16 N6 O2; Mol wt: 228.2544

ACTION – Antineoplastic agent, an analogue of trimelamol with comparable activity but greatly improved stability, particularly useful for the treatment of ovarian cancers including cisplatin-resistant cancers. *In vitro*, compound exhibited IC₅₀ values of 25.1, 10.7, 14.7 and 35.8 μM, respectively, against murine plasmacytoma PC6, rat mammary carcinoma Walker 256, human small cell lung cancer H69 and human epithelial ovarian cancer CH1 cells, compared to respective IC₅₀ values of 12.9, 9.4, 8.5 and 23.4 μM for trimelamol. *In vivo*, it was shown to inhibit tumor growth in mice bearing ADJ/PC6 tumors with comparable potency to trimelamol and a greater therapeutic index; comparable efficacy to trimelamol was also observed in mice bearing human ovarian cancer PXN65 xenografts. Another compound from this series of melamine derivatives is:



CB-7683 [271450]: C11 H13 F9 N6 O2

SOURCE – Cancer Research Campaign Technology.

REFERENCES

1. Jarman, M. and Coley, H.M. (Cancer Research Campaign Technology Ltd.) *Melamine derivs. for use in the treatment of cancer*. US 5854244.

CANCER GENE THERAPY**HYB-0432****271044**

30-Mer antisense phosphorothioate 2'-MeO oligoribonucleotide whose sequence is:
5'-AGCCGGCCACAGGCAUGGCGGCGGGCGG-3'

ACTION – Antisense phosphorothioate oligonucleotide specific for thymidylate synthase (TS) for use in downregulating TS mRNA translation or protein expression, resulting in growth inhibition of malignant tumors; additionally, it can be used to prevent or overcome resistance to TS inhibitors. Results of *in vitro* tests showed that compound inhibits human TS mRNA translation in rabbit reticulocyte lysates in a highly specific manner. Additionally, it was shown to inhibit TS expression in human breast cancer MCF-7 cells and was found to inhibit the growth of MCF-7 cells in a concentration-dependent manner when formulated in liposomes.

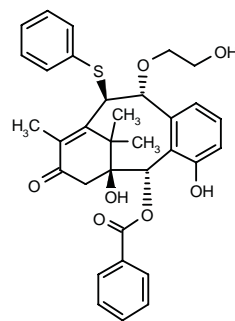
SOURCE – Hybridon.

REFERENCES

1. Schmitz, J.C. et al. (Hybridon, Inc.) *Antisense oligonucleotides specific for thymidylate synthase*. WO 9849287.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS**270079**

[5S-(5α,6β,11β,12α)]-5-(Benzoyloxy)-4,6-dihydroxy-12-(2-hydroxyethoxy)-9,13,13-trimethyl-11-(phenylsulfanyl)-5,6,7,8,11,12-hexahydro-6,10-methanocyclodecen-8-one



C33 H34 O7 S; Mol wt: 574.6906

ACTION – Multidrug resistance (MDR)-reversing agent, a C-aromatic taxoid that is able to inhibit cellular drug efflux mediated by P-glycoprotein. In ovarian MDR 2780AD cancer cells, compound (1-10 µg/ml) exhibited potency comparable to verapamil in enhancing intracellular vincristine accumulation.

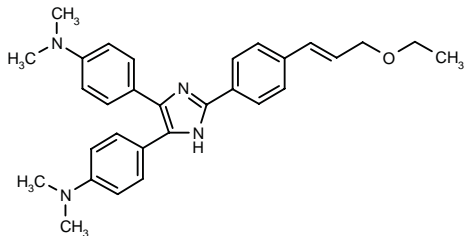
SOURCES – Tokyo Institute of Technology, Tokyo (JP); University of Tokyo, Tokyo (JP).

REFERENCES

1. Morihira, K. et al. *Synthesis of C-ring aromatic taxoids and evaluation of their multi-drug resistance reversing activity.* Bioorg Med Chem Lett 1998, 8(21): 2973.

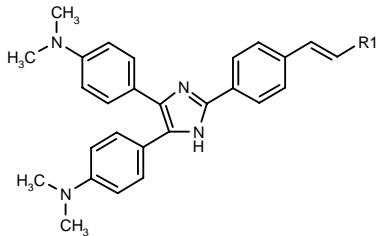
270941

4,4'-[2-[4-[3-Ethoxy-1(E)-propenyl]phenyl]-1H-imidazole-4,5-diyl]bis(N,N-dimethylaniline)



C30 H34 N4 O; Mol wt: 466.6256

ACTION – Multidrug resistance (MDR) modulator that potentiates the sensitivity of cancer cells to antitumor drugs such as doxorubicin (DOX), vinblastine (VLB) and paclitaxel. In particular, the effective concentration (EC₅₀) of compound required to enhance the cytotoxicity of VLB in the MDR cell line CEM/VLB1000 was 0.098 µM. Within this series of specifically claimed imidazole derivatives, the following are also included:



Compound	R1	Formula
270942	CH2OMe	C ₂₉ H ₃₂ N ₄ O
270943	CH2OPh	C ₃₄ H ₃₄ N ₄ O
270944	CON(Me) ₂	C ₃₀ H ₃₃ N ₅ O
270945	CH2OH	C ₂₈ H ₃₀ N ₄ O

SOURCE – Ontogen.

REFERENCES

1. Mjalli, A.M.M. and Zhang, C. (Ontogen Corp.) *Imidazole derivs. as MDR modulators.* US 5840721, WO 9902155.

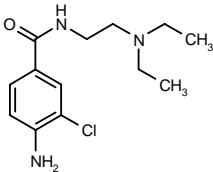
DECLOPRAMIDE

Prop INN

236927

4-Amino-3-chloro-N-[2-(diethylamino)ethyl]benzamide

Oxi-104



C13 H20 Cl N3 O; Mol wt: 269.7740

ACTION – Third-generation DNA repair inhibitor from the N-substituted benzamide class that causes cell death by two different mechanisms involving caspase and NFκB. It induces apoptosis in tumor cell lines and enhances apoptosis associated with conventional cancer treatments. Compound is currently in phase I/II clinical trials as a chemosensitizer in combination with 5-FU or cisplatin in patients with advanced-stage cancer. It is also potentially useful as a radiation sensitizer.

SOURCE – OxiGene.

REFERENCES

1. Pero, R.W. et al. (OxiGene, Inc.) *Use of aryl N-substituted carboxamides to kill tumors.* WO 9732576.

2. Pero, R.W. et al. (Oxigene, Inc.). *Compositions and use of benzamides and nicotinamides as anti-inflammatory agents.* WO 9732582.

3. Hua, J. et al. *Pharmacokinetics and central nervous system toxicity of declopramide (3-chloroprocaïnamide) in rats and mice.* Anti-Cancer Drugs 1999, 10(1): 79.

4. Hua, J. and Pero, R.W. *Toxicity antitumor and chemosensitizing effects of 3-chloroprocaïnamide.* Acta Oncol 1997, 36(8): 811.

5. Pero, R.W. et al. *Multiple mechanisms of action of the benzamides and nicotinamides as sensitizers of radiotherapy: Oportunities for drug design.* Cancer Detect Prev 1998, 22(3): 225.

6. *Company Profile: Oxigene.* Prous Science Daily Essentials 1997, Nov 28.

7. *Oxigene announces pre-clinical studies into TNF-α inhibition.* Oxigene, Inc. Press Release 1997, March 13.

8. *Oxigene announces start of clinical testing of chemosensitiser OXI-104.* Oxigene, Inc. Press Release 1997, May 6.

9. *Oxigene describes mechanism of action, therapeutic potential of declopramide.* Prous Science Daily Essentials 1998, Dec 15.

10. *Oxigene Inc. to initiate clinical trial for Oxi-104.* Oxigene, Inc. Press Release 1996, Aug 13.

11. *Oxigene signs collaborative agreement with Boston Medical Center.* Oxigene, Inc. Press Release 1997, Jan 7.

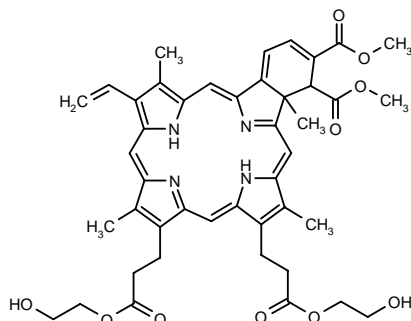
12. *OxiGENE: Q3 1997 highlights.* Prous Science Daily Essentials 1997, Oct 28.

13. *Proposed international nonproprietary names (Prop. INN): List 78.* WHO Drug Inf 1997, 11(4): 270.

PHOTOSENSITIZERS

271523

3,8,12,18-Tetramethyl-2-vinyl-13,17-bis[2-(2-hydroxyethoxycarbonyl)ethyl]-7⁴,8-dihydro-21*H*,23*H*-benzo[*g*]porphyrin-7³,7⁴-dicarboxylic acid dimethyl ester



C44 H48 N4 O10; Mol wt: 792.8812

ACTION – Photoactive agent for use in photodynamic therapy (PDT), found to exhibit higher *in vitro* cytotoxicity following exposure to light than the known agent BPD-MA (verteporfin) in L1210 and dendritic D2SC/1 cells in the presence of serum. In addition, it exhibited stronger activation of the stress pathway kinases c-jun and HSP27, and stronger inhibition of the mitogenic pathway kinase p70 S6K than BPD-MA, and it was also found to be more potent than this compound in activating caspases in HL-60 cells. When given to mice bearing M1 tumors at 1 mg/kg i.v. followed by laser light irradiation, it was at least as effective as BPD-MA at the same dose. In addition, it exhibited stronger immunomodulatory activity than BPD-MA, as demonstrated by 59% inhibition of antigen-induced ear swelling in mice at 0.3 mg/kg i.v. compared to 49% inhibition for BPD-MA at 1.0 mg/kg i.v.

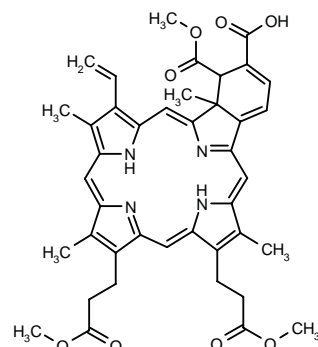
SOURCES – University of British Columbia, Vancouver, BC (CA); QLT PhotoTherapeutics.

REFERENCES

1. Sternberg, E. et al. (QLT PhotoTherapeutics Inc.;University of British Columbia) *Ethylene glycol esters of monohydrobenzoporphyrin derivs. as photoactive agents*. WO 9850387.

271526

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-3-vinyl-7,7²-dihydro-21*H*,23*H*-benzo[*g*]porphyrin-7¹,7²-dicarboxylic acid 7¹-monomethyl ester



C41 H42 N4 O8; Mol wt: 718.8028

ACTION – Photoactive agent for use in photodynamic therapy (PDT), found to be a very potent photosensitizer of murine leukemia L1210 cells *in vitro* (LD₅₀ = 7 and 35 ng/ml incubating the cells with compound for 1 h in the absence or presence of serum, respectively, followed by exposure to broad-spectrum light). Compound exhibited very rapid pharmacokinetics (i.e., very rapid uptake and clearance) both *in vitro* in L1210 cells and *in vivo* in normal and tumor-bearing mice, thus avoiding the side effect of prolonged skin hypersensitivity. When given to rhabdomyosarcoma M1-bearing mice, compound was found to preferentially accumulate in tumor and lymph nodes as compared to skin and muscle. A representative compound from a novel series of monohydrobenzoporphyrin derivatives.

SOURCES – University of British Columbia, Vancouver, BC (CA); QLT PhotoTherapeutics.

REFERENCES

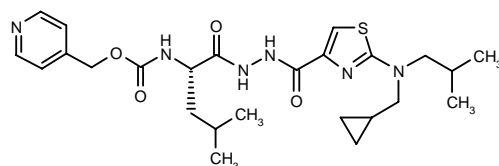
1. Sternberg, E. et al. (QLT PhotoTherapeutics Inc.;University of British Columbia) *A new class of benzoporphyrin deriv. photoactive cpds.*. US 5880145, WO 9850386.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

270919

N'-[2-[*N*-(Cyclopropylmethyl)-*N*-isobutylamino]thiazol-4-ylcarbonyl]-*N'*-(4-pyridylmethoxycarbonyl)-L-leucylhydrazide

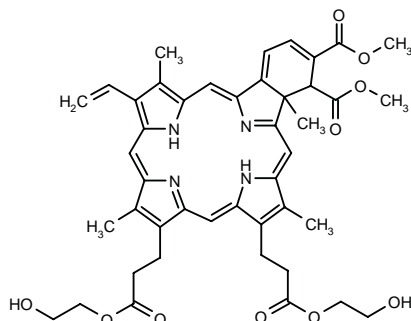


C25 H36 N6 O4 S; Mol wt: 516.6634

PHOTOSENSITIZERS

271523

3,8,12,18-Tetramethyl-2-vinyl-13,17-bis[2-(2-hydroxyethoxycarbonyl)ethyl]-7⁴,8-dihydro-21*H*,23*H*-benzo[*g*]porphyrin-7³,7⁴-dicarboxylic acid dimethyl ester



C44 H48 N4 O10; Mol wt: 792.8812

ACTION – Photoactive agent for use in photodynamic therapy (PDT), found to exhibit higher *in vitro* cytotoxicity following exposure to light than the known agent BPD-MA (verteporfin) in L1210 and dendritic D2SC/1 cells in the presence of serum. In addition, it exhibited stronger activation of the stress pathway kinases c-jun and HSP27, and stronger inhibition of the mitogenic pathway kinase p70 S6K than BPD-MA, and it was also found to be more potent than this compound in activating caspases in HL-60 cells. When given to mice bearing M1 tumors at 1 mg/kg i.v. followed by laser light irradiation, it was at least as effective as BPD-MA at the same dose. In addition, it exhibited stronger immunomodulatory activity than BPD-MA, as demonstrated by 59% inhibition of antigen-induced ear swelling in mice at 0.3 mg/kg i.v. compared to 49% inhibition for BPD-MA at 1.0 mg/kg i.v.

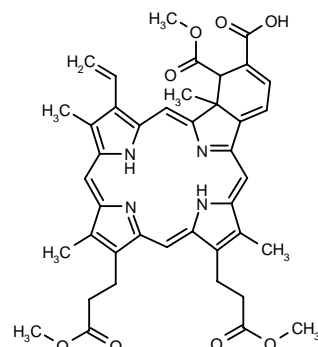
SOURCES – University of British Columbia, Vancouver, BC (CA); QLT PhotoTherapeutics.

REFERENCES

1. Sternberg, E. et al. (QLT PhotoTherapeutics Inc.;University of British Columbia) *Ethylene glycol esters of monohydrobenzoporphyrin derivs. as photoactive agents*. WO 9850387.

271526

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-3-vinyl-7²,8-dihydro-21*H*,23*H*-benzo[*g*]porphyrin-7¹,7²-dicarboxylic acid 7¹-monomethyl ester



C41 H42 N4 O8; Mol wt: 718.8028

ACTION – Photoactive agent for use in photodynamic therapy (PDT), found to be a very potent photosensitizer of murine leukemia L1210 cells *in vitro* (LD₅₀ = 7 and 35 ng/ml incubating the cells with compound for 1 h in the absence or presence of serum, respectively, followed by exposure to broad-spectrum light). Compound exhibited very rapid pharmacokinetics (i.e., very rapid uptake and clearance) both *in vitro* in L1210 cells and *in vivo* in normal and tumor-bearing mice, thus avoiding the side effect of prolonged skin hypersensitivity. When given to rhabdomyosarcoma M1-bearing mice, compound was found to preferentially accumulate in tumor and lymph nodes as compared to skin and muscle. A representative compound from a novel series of monohydrobenzoporphyrin derivatives.

SOURCES – University of British Columbia, Vancouver, BC (CA); QLT PhotoTherapeutics.

REFERENCES

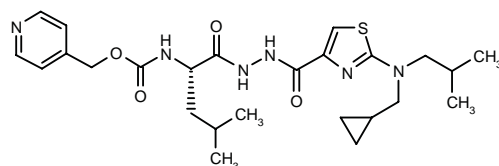
1. Sternberg, E. et al. (QLT PhotoTherapeutics Inc.;University of British Columbia) *A new class of benzoporphyrin deriv. photoactive cpds.* US 5880145, WO 9850386.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

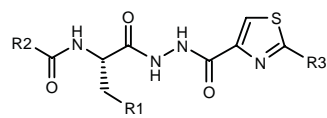
270919

N'-[2-[*N*-(Cyclopropylmethyl)-*N*-isobutylamino]thiazol-4-ylcarbonyl]-*N*^α-(4-pyridylmethoxycarbonyl)-L-leucylhydrazide

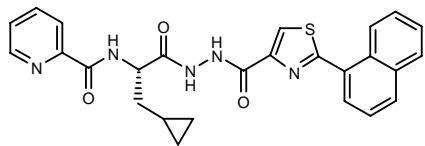


C25 H36 N6 O4 S; Mol wt: 516.6634

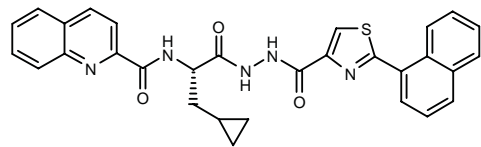
ACTION – Agent for the treatment of diseases characterized by excessive bone or cartilage loss such as osteoporosis, periodontitis and arthritis, an inhibitor of cysteine proteases, particularly cathepsin K. Within this series of specifically claimed heterocycleketohydrazide derivatives, the following are also included:



Compound	R1	R2	R3	Formula
270920	i-Pr	3-Pyr-CH2O	1-Naph	C ₂₇ H ₂₇ N ₅ O ₄ S
270921	i-Pr	2-Pyr-CH2O	N(i-Bu)2	C ₂₅ H ₂₈ N ₆ O ₄ S
270922	i-Pr	4-Pyr-CH2O	9-phenanthrenyl	C ₃₁ H ₂₅ N ₅ O ₄ S
270923	i-Pr	4-(t-BuOCO)- -PhCH2O	N(i-Bu)Ph	C ₃₃ H ₄₃ N ₅ O ₆ S
270924	i-Pr	3-quinoliny	1-Naph	C ₃₀ H ₂₇ N ₅ O ₃ S
270925	i-Pr	3-Me-4-Pyr	1-Naph	C ₂₇ H ₂₇ N ₅ O ₃ S
270926	i-Pr	6-Me-3-Pyr	cyclopropyl- CH2N(cyclopropyl)	C ₂₄ H ₃₂ N ₆ O ₃ S
270927	Et	OCH2Ph	1-Naph	C ₂₇ H ₂₆ N ₄ O ₄ S
270928	i-Pr	6-Me-3-Pyr	1-Naph	C ₂₇ H ₂₇ N ₅ O ₃ S
270931	Pr	5-Me-4-imidazolyl	1-Naph	C ₂₅ H ₂₆ N ₆ O ₃ S
270932	Pr	6-Me-3-Pyr	1-Naph	C ₂₇ H ₂₇ N ₅ O ₃ S
270933	Et	2-quinoliny	1-Naph	C ₂₉ H ₂₅ N ₅ O ₃ S
270934	i-Pr	4-F-Ph	1-Naph	C ₂₇ H ₂₅ FN ₄ O ₃ S
270935	t-Bu	5-Bu-2-Pyr	cyclopropyl- CH2N(cyclopropyl)	C ₂₈ H ₄₀ N ₆ O ₃ S



270929: C₂₆ H₂₃ N₅ O₃ S



270930: C₃₀ H₂₅ N₅ O₃ S

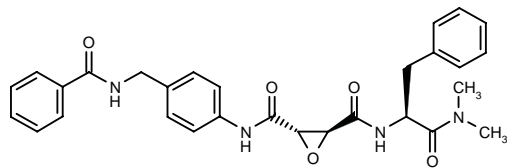
SOURCE – SmithKline Beecham.

REFERENCES

1. Halbert, S.M. et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9848799.

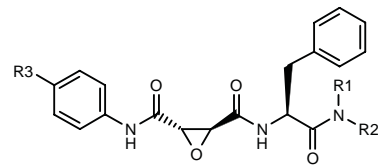
271022

(2*S*,3*S*)-*N*²-[4-(Benzamidomethyl)phenyl]-*N*³-[1(*S*)-(N,N-dimethylcarbamoyl)-2-phenylethyl]oxirane-2,3-dicarboxamide



C₂₉ H₃₀ N₄ O₅; Mol wt: 514.5790

ACTION – Agent for the treatment of osteoporosis, hypercalcemia and other bone metabolism disorders, a selective inhibitor of cathepsin L, as demonstrated by IC₅₀ values of 6.0 nM and 77 μM, respectively, against cathepsin L and B from rat liver. Other compounds from this series of epoxysuccinamide derivatives include the following:



Compound	R1	R2	R3	Formula
271023	CH2CH2Ph	H	t-BuOCONHCH2	C ₃₃ H ₃₈ N ₄ O ₆
271024	Me	Me	Et	C ₂₃ H ₂₇ N ₃ O ₄
271025	Me	Me	OPh	C ₂₇ H ₂₇ N ₃ O ₅

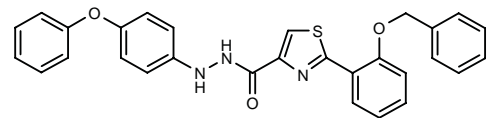
SOURCE – Taiho.

REFERENCES

1. Asao, T. et al. (Taiho Pharmaceutical Co., Ltd.) *Novel epoxysuccinamide derivs. or salts thereof*. WO 9847887.

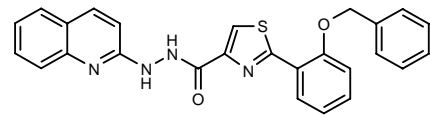
271054

2-[2-(Benzyloxy)phenyl]-*N*'-(4-phenoxyphenyl)thiazole-4-carbohydrazide



C₂₉ H₂₃ N₃ O₃ S; Mol wt: 493.5847

ACTION – An inhibitor of cysteine proteases, particularly cathepsin K, with potential in the treatment of disorders involving excessive bone loss or cartilage or matrix degradation such as osteoporosis, gingivitis, periodontal disease, rheumatoid arthritis and osteoarthritis. Another specifically claimed compound from this series of thiazoloketohydrazide derivatives is:



271055: C₂₆ H₂₀ N₄ O₂ S

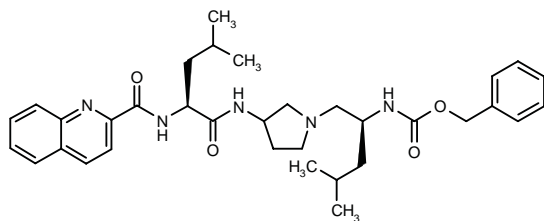
SOURCE – SmithKline Beecham.

REFERENCES

1. DesJarlais, R.L. et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9849152.

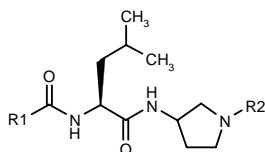
271594

*N*¹-[1-[2(*S*)-(Benzyloxycarbonylamino)-4-methylpentyl]pyrrolidin-3-yl]-*N*²-(2-quinolinylicarbonyl)-*L*-leucinamide

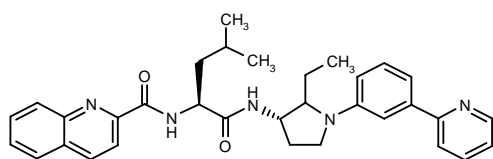


C34 H45 N5 O4; Mol wt: 587.7605

ACTION – An inhibitor of cysteine proteases, particularly cathepsin K, with potential in the treatment of diseases involving excessive bone or cartilage loss such as osteoporosis, periodontitis, rheumatoid arthritis and osteoarthritis. Other specifically claimed compounds within this series of pyrrolidiny derivatives include the following:



Compound	R1	R2	Isomer	Formula
271596	2-Naph	(<i>S</i>)-CH ₂ CH(<i>i</i> -Bu)-NHCO ₂ CH ₂ Ph	R	C ₃₅ H ₄₆ N ₄ O ₄
271599	4-Pyr-CH ₂ O	1-adamantyl-CO	R	C ₂₈ H ₄₀ N ₄ O ₄
271600	2-benzo-thienyl	(<i>S</i>)-CH ₂ CH(<i>i</i> -Bu)-NHCO ₂ CH ₂ Ph	R	C ₃₃ H ₄₄ N ₄ O ₄ S
271602	5-Cl-2-benzofuryl	(<i>S</i>)-CH ₂ CH(<i>i</i> -Bu)-NHCO ₂ CH ₂ Ph	R	C ₃₃ H ₄₃ ClN ₄ O ₅
271603	6-benzo-thiazolyl	(<i>S</i>)-CH ₂ CH(<i>i</i> -Bu)-NHCO ₂ CH ₂ Ph	S	C ₃₂ H ₄₃ N ₅ O ₄ S
271604	2-indolyl	(<i>S</i>)-CH ₂ CH(<i>i</i> -Bu)-NHCO ₂ CH ₂ Ph	S	C ₃₃ H ₄₅ N ₅ O ₄
271606	<i>t</i> -BuO	4-CN-PhCH ₂	S	C ₂₃ H ₃₄ N ₄ O ₃
271608	2-Naph	3-furyl-CH ₂	S	C ₂₆ H ₃₁ N ₃ O ₃



271598: C33 H37 N5 O2

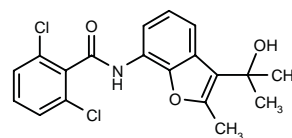
SOURCE – SmithKline Beecham.

REFERENCES

1. Marquis, R.W. et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9850534.

FR-167356**270162**

2,6-Dichloro-*N*-[3-(1-hydroxy-1-methylethyl)-2-methyl-1-benzofuran-7-yl]benzamide



C19 H17 Cl₂ N O₃; Mol wt: 378.2533

ACTION – Bone resorption inhibitor that acts by inhibiting osteoclast vacuolar ATPase (V-ATPase; IC₅₀ = 210 nM). It prevented excessive bone resorption in ovariectomized rats (70% at a dose of 32 mg/kg p.o. b.i.d.). Potentially useful in the treatment of postmenopausal osteoporosis.

SOURCE – Fujisawa.

REFERENCES

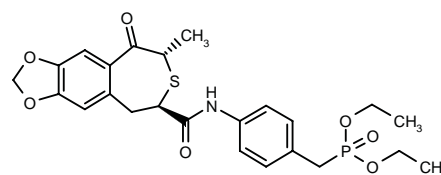
1. Kawai, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzofuran derivs. useful as inhibitors of bone resorption*. EP 757682, JP 97512795, US 5858995, WO 9529907.

2. Yamazaki, H. et al. *Synthesis and pharmacological activities of novel benzofuran derivatives as vacuolar type H⁺-ATPase inhibitors*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-32.

TAK-778***238898**

(2*R*,4*S*)-(-)-*N*-[4-(Diethoxyphosphorylmethyl)phenyl]-4-methyl-7,8-(methylenedioxy)-5-oxo-1,2,4,5-tetrahydro-3-benzothiepine-2-carboxamide

(6*R*,8*S*)-(-)-*N*-[4-(Diethoxyphosphorylmethyl)phenyl]-8-methyl-9-oxo-5,6,8,9-tetrahydrothiepine[4,5-*f*]-1,3-benzodioxole-6-carboxamide



C24 H28 N O7 P S; Mol wt: 505.5252

ACTION – Compound that stimulates bone formation, as indicated by its ability to significantly increase cellular alkaline phosphatase (ALP) activity in rat bone marrow stromal cells at concentrations of 1-10 μM, being more active than ipriflavone. Compound also stimulated ALP activity in the mouse osteoblastic cell line MC3T3-E1 and enhanced the effect of bone morphogenetic protein (BMP) in these cells. A sustained-release formulation of the compound was reported to stimulate the repair of a rat skull defect. It was selected for further investigation as a potential therapeutic agent for the treatment of osteoporosis and bone fractures.

SOURCE – Takeda.

REFERENCES

1. Hoshino, T. et al. (Takeda Chemical Industries, Ltd.) *Osteogenetic promoting pharmaceutical compsn*. JP 97263545, WO 9639134.

2. Hoshino, T. et al. (Takeda Chemical Industries, Ltd.) *Pharmaceutical compsn. containing osteogenesis-promoting substance and a polyethylene glycol*. WO 9808517.

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4. Oda, T. et al. *Synthesis of novel 2-benzothiopyran and 3-benzothiepin derivatives and their stimulatory effect on bone formation*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.255.

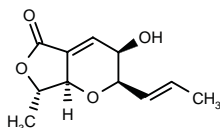
5. Oda, T. et al. *Synthesis of novel 2-benzothiopyran and 3-benzothiepin derivatives and their stimulatory effect on bone formation*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-31.

*Identified compound **238898** Drug Data Report 1996, 018(10): 0936.

TAN-2483A

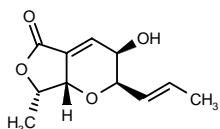
271399

(2*R*,3*R*,7*S*,7*aR*)-3-Hydroxy-7-methyl-2-[1(*E*)-propenyl]-3,5,7,7*a*-tetrahydro-2*H*-furo[3,4-*b*]pyran-5-one



C11 H14 O4; Mol wt: 210.2276

ACTION – Agent for the treatment of bone disorders, cancer and inflammatory disorders such as rheumatoid arthritis, osteoarthritis and pancreatitis, a tyrosine kinase inhibitor isolated from a culture of a filamentous fungus NF2329 (FERM BP-5905). It inhibited human recombinant c-src kinase activity with an IC₅₀ value of 4 μM. In addition, it gave 76% inhibition of parathyroid hormone (PTH)-induced bone resorption in murine femoral bone preparations at a concentration of 10 μM. Another related compound is:



TAN-2483B [271400]: C11 H14 O4

SOURCE – Takeda.

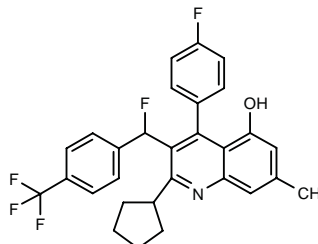
REFERENCES

1. Hayashi, K. et al. (Takeda Chemical Industries, Ltd.) *TAN-2483 related cpds., their preparation method and their use*. JP 98287679.

TREATMENT OF LIPOPROTEIN DISORDERS

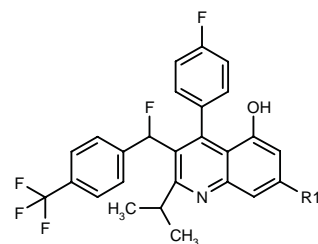
270884

2-Cyclopentyl-4-(4-fluorophenyl)-3-[1-fluoro-1-[4-(trifluoromethyl)phenyl]methyl]-7-methyl-5-quinolinol



C29 H24 F5 N O; Mol wt: 497.5046

ACTION – Agent for the treatment of dyslipidemia, hypertriglyceridemia, hyperlipidemia and arteriosclerosis, a potent inhibitor of cholesteryl ester transfer protein (CETP; IC₅₀ = 180 nM). Other compounds from this series of 5-oxysubstituted quinoline derivatives include the following:



Compound	R1	Formula
270886	3-CF3-Ph	C ₃₃ H ₂₃ F ₈ NO
270887	H	C ₂₆ H ₂₀ F ₅ NO

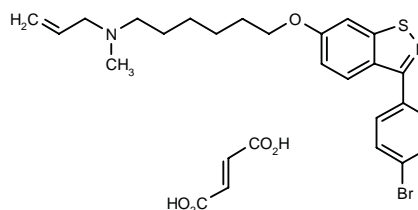
SOURCE – Bayer.

REFERENCES

1. Müller-Gliemann, M. et al. (Bayer AG) *5-Oxysubst. chinolines and their use as cholesterol ester transfer proteins inhibitors*. WO 9839299.

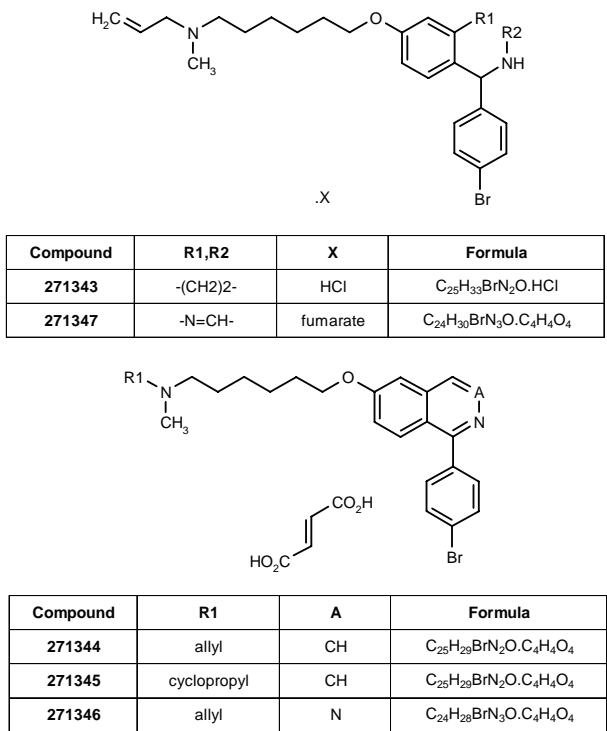
271342

N-Allyl-*N*-[6-[3-(4-bromophenyl)benzothiazol-6-yloxy]hexyl]-*N*-methylamine fumarate



C23 H27 Br N2 O S . C4 H4 O4; Mol wt: 575.5209

ACTION – Hypolipidemic and antifungal agent that inhibits cholesterol biosynthesis through inhibition of lanosterol synthase (IC_{50} = 3.3 nM in human liver microsomes). *In vivo*, it was shown to lower total cholesterol by 33%, LDL cholesterol by 36% and HDL cholesterol by 27% in cholesterol-fed hamsters when administered at 200 μ mol mixed with the diet. Antifungal activity was demonstrated *in vitro* against *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus* (IC_{50} < 0.32, < 0.32 and 3.90 mg/ml, respectively). A representative compound from a series of aminoalkyl-substituted heterobicyclic derivatives, wherein the following are also included:



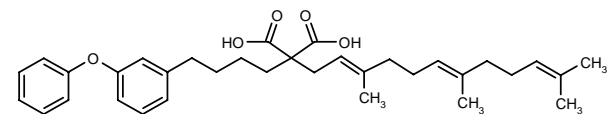
SOURCE – Roche.

REFERENCES

1. Aebi, J. et al. (Hoffmann-La Roche, Inc.) *Aminoalkyl-substd. benzoheterocyclic cpds.* US 5856503.

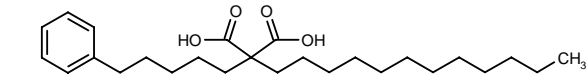
271401

2-[4-(3-Phenoxyphenyl)butyl]-2-[3,7,11-trimethyl-2(E),6(E),10-dodecatrienyl]malonic acid



C34 H44 O5; Mol wt: 532.7166

ACTION – Hypolipidemic, hypocholesterolemic and antifungal agent with squalene synthase-inhibitory activity (IC_{50} = 0.45, 0.124 and 0.63 μ g/ml, respectively, against enzyme from *Aspergillus fumigatus* 1776, *Candida albicans* 1768 and rat liver). In addition, compound was shown to inhibit cholesterol biosynthesis *in vitro* in HepG2 cells (IC_{50} = 36.1 μ g/ml). Another compound from this series of malonic acid derivatives is:



271402: C26 H42 O4

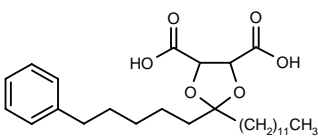
SOURCE – Nippon Kayaku.

REFERENCES

1. Ichikawa, Y. et al. (Nippon Kayaku Co., Ltd.) *Squalene synthase inhibitors and novel malonic acid derivs.* JP 98298134.

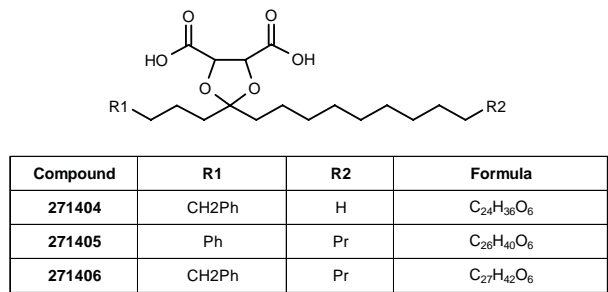
271403

2-Dodecyl-2-(5-phenylpentyl)-1,3-dioxolane-4,5-dicarboxylic acid



C28 H44 O6; Mol wt: 476.6496

ACTION – Hypolipidemic agent that acts by inhibiting squalene synthase (IC_{50} = 0.58, 0.69 and 4.47 μ g/ml, respectively, against enzyme isolated from *Aspergillus fumigatus* 1776, *Candida albicans* 1768 and rat liver). Antifungal activity was demonstrated against *A. fumigatus* 1776 (IC_{50} = 16.16 μ g/ml) and *C. albicans* 1768 (IC_{50} = 3.18 μ g/ml). Other representative compounds within this series of tartaric acid derivatives include the following:



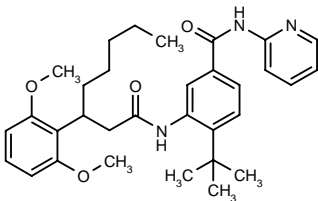
SOURCE – Nippon Kayaku.

REFERENCES

1. Ichikawa, Y. et al. (Nippon Kayaku Co., Ltd.) *Novel tartaric acid derivs., their use and preparation method.* JP 98298177.

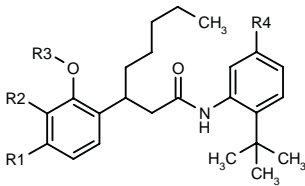
271554

4-(tert-Butyl)-3-[3-(2,6-dimethoxyphenyl)octanamido]-N-(2-pyridinyl)benzamide



C32 H41 N3 O4; Mol wt: 531.6929

ACTION – Hypolipidemic and antiatherosclerotic agent with ACAT-inhibitory activity (IC₅₀ = 0.73 ng/ml using enzyme from murine macrophages). Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
271555	OMe	H	Me	CH2NHSO2Et	C ₂₉ H ₄₄ N ₂ O ₅ S
271557	OMe	H	Me	CH2NHCON(Me)2	C ₃₀ H ₄₅ N ₃ O ₄
271558	OMe	H	Me	3-Pyr-CONHCO	C ₃₃ H ₄₁ N ₃ O ₅
271559	OMe	H	Me	3-Pyr-CONHCH2	C ₃₃ H ₄₃ N ₃ O ₄
271560	H	-OCH2CH2-		i-PrNHCONHCH2	C ₃₁ H ₄₅ N ₃ O ₄

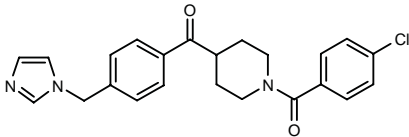
SOURCE – Sankyo.

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1. Yoshida, A. et al. (Sankyo Co., Ltd.) *Anti-arteriosclerosis agents*. JP 98316562.

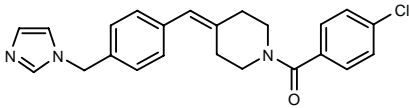
271657

1-[1-(4-Chlorobenzoyl)piperidin-4-yl]-1-[4-(imidazol-1-ylmethyl)phenyl]methanone



C23 H22 Cl N3 O2; Mol wt: 407.8988

ACTION – Hypolipidemic agent that prevents cholesterol biosynthesis by inhibiting the activity of lanosterol synthase, as demonstrated in rat liver microsomes (IC₅₀ = 0.044 μM). Cholesterol biosynthesis-inhibitory effects were also demonstrated *in vivo* in mice, with an ID₅₀ value of 2.4 mg/kg p.o. LD₅₀ > 2000 mg/kg p.o. in mice. Another representative compound within this series of imidazolylmethylphenyl or pyridylmethylphenyl derivatives is:



271658: C23 H22 Cl N3 O

SOURCE – Nippon Soda.

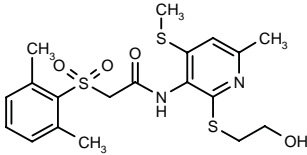
REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Imidazolylmethylphenyl or pyridylmethylphenyl derivs. and their preparation method*. JP 98287671.

J-104127

270161

2-(2,6-Dimethylphenylsulfonyl)-N-[2-(2-hydroxyethylsulfonyl)-6-methyl-4-(methylsulfonyl)-3-pyridinyl]acetamide



C19 H24 N2 O4 S3; Mol wt: 440.6066

ACTION – Potent and selective ACAT inhibitor with IC₅₀ values of 7.9 nM against enzyme from HepG2 cells and 8.9 nM against enzyme from rat liver. Compound exhibited potent hypocholesterolemic activity in rats and hamsters and good bioavailability.

SOURCE – Banyu.

REFERENCES

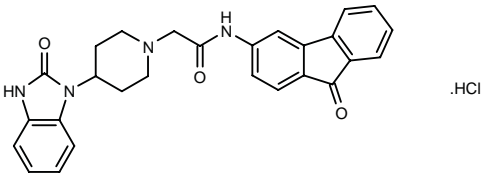
1. Ishikawa, K. et al. (Banyu Pharmaceutical Co., Ltd.) *Arylthioacetamide derivs*. WO 9626925.

2. Naya, A. et al. *N-Pyridyl(phenylsulfonyl)acetamide derivatives: Potent ACAT inhibitors*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-06.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

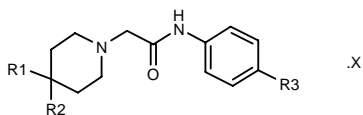
271246

2-[4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]-N-(9-oxo-9H-fluoren-3-yl)acetamide hydrochloride

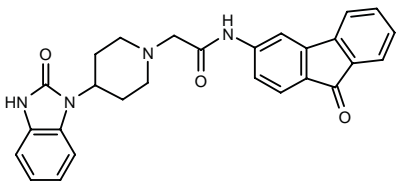


C27 H24 N4 O3 . HCl; Mol wt: 488.9725

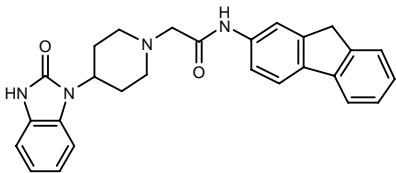
ACTION – A potent and selective neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated in binding studies by K_i values of > 5, > 5, > 5, 0.00047 and 0.00034 μM for inhibition of [¹²⁵I]-PYY binding to human Y₁, Y₂, Y₄ and Y₅ receptors and rat Y₅ receptors, respectively; Compound acted as a Y₅ antagonist in a functional assay, as demonstrated by its ability to block NPY-induced inhibition of cAMP accumulation in forskolin-stimulated cells expressing the rat Y₅ receptor (95% inhibition at 10 μM). Potentially useful for the treatment of obesity, bulimia, type II diabetes, hyperlipidemia, sleep apnea, depression, epilepsy and hypertension. Other compounds from this series of amide derivatives include the following:



Compound	R1	R2	R3	X	Formula
271247	NHMe	CONH2	COPh		C ₂₂ H ₂₆ N ₄ O ₃
271248	H	4-CN-PhCH2	COPh		C ₂₈ H ₂₇ N ₃ O ₂
271249	Ph	COEt	COPh		C ₂₉ H ₃₀ N ₂ O ₃
271250	Ph	COPr	C6H11		C ₂₉ H ₃₈ N ₂ O ₂
271251	Ph	Ac	COPh		C ₂₈ H ₂₈ N ₂ O ₃
271252	Ph	Ac	C6H11		C ₂₇ H ₃₄ N ₂ O ₂
271253	H	2-oxo-2,3-dihydro-1-benzimidazolyl	C6H11		C ₂₆ H ₃₂ N ₄ O ₂
271254	H	2-oxo-2,3-dihydro-1-benzimidazolyl	COPh	HCl	C ₂₇ H ₂₆ N ₄ O ₃ .HCl
271255	H	2-oxo-2,3-dihydro-1-benzimidazolyl	COCH2-Ph	HCl	C ₂₈ H ₂₈ N ₄ O ₃ .HCl
271257	Ph	CN	C6H11	HCl	C ₂₆ H ₃₁ N ₃ O.HCl
271258	CONH2	NHEt	C6H11	oxalate	C ₂₂ H ₃₄ N ₄ O ₂ .C ₂ H ₂ O ₄
271259	COEt	Ph	C6H11	HCl	C ₂₈ H ₃₆ N ₂ O ₂ .HCl



271256: C27 H24 N4 O3



271260: C27 H26 N4 O2

SOURCE – Bayer.

REFERENCES

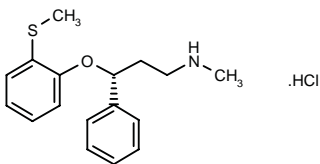
1. Connell, R.D. et al. (Bayer Corp.) *Amide derivs. as selective neuropeptide Y receptor antagonists*. WO 9835957.

LY-368975

270165

(R)-N-Methyl-3-[2-(methylsulfanyl)phenoxy]-3-phenyl-propylamine hydrochloride

(R)-Thionisoxetine



C17 H21 N O S . HCl; Mol wt: 323.8858

ACTION – A selective norepinephrine (NE) reuptake inhibitor ($K_i = 1.3$ nM) with improved potency and selectivity compared to tomoxetine and nisoxetine. *Ex vivo* in rats, it inhibited [³H]-NE uptake into hypothalamic synaptosomes with an ED₅₀ of 2.5 mg/kg p.o. and [³H]-tomoxetine binding to the NE transporter with an ED₅₀ of 2.7 mg/kg p.o. Compound prevented cardiac NE depletion induced in mice by 6-hydroxydopamine (ED₅₀ = 1.22 mg/kg p.o.). In 18-h food-deprived rats, compound at a dose of 10 mg/kg s.c. suppressed food intake until 4 h after reintroduction of food, and in nonfasted rats trained to drink sweetened condensed milk, it produced a significant dose-dependent decrease in consumption (44% at 3 mg/kg). No effect was observed on locomotor behavior in mice over the dose range 0.1-10 mg/kg p.o. Potentially useful in the treatment of obesity and eating disorders.

SOURCE – Lilly.

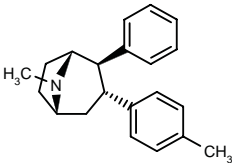
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- 1. Gehlert, D.R. et al. (Eli Lilly and Company) *N-Alkyl-3-phenyl-3-(2-alkyl-thiophenoxy)propylamines*. EP 591581.
- 2. Gehlert, D.R. et al. *The selective norepinephrine reuptake inhibitor, LY368975, reduces food consumption in animal models of feeding*. J Pharmacol Exp Ther 1998, 287(1): 122.

TREATMENT OF POISONING AND DRUG DEPENDENCY

270818

(1R,2R,3R,5S)-8-Methyl-3-(4-methylphenyl)-2-phenyl-8-azabicyclo[3.2.1]octane



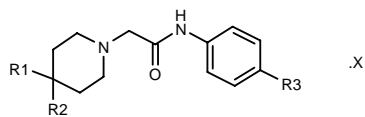
C21 H25 N; Mol wt: 291.4355

ACTION – Cocaine analogue that adopts the boat conformation and exhibits high affinity for the dopamine transporter (DAT; $K_i = 2.87$ nM for displacement of [³H]-mazindol binding in rat striatal membranes) and high selectivity over the 5-HT transporter ($K_i = 173$ nM for displacement of [³H]-paroxetine binding in rat striatal membranes). It also potently inhibited dopamine uptake ($K_i = 4.16$ nM), showing much weaker activity against 5-HT uptake ($K_i = 287$ nM). It is currently undergoing studies in drug discrimination paradigms in animals.

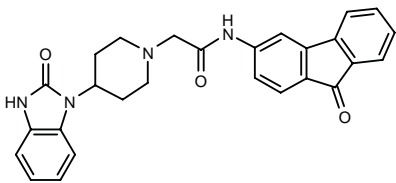
SOURCES – Georgetown University Medical Center, Washington, D.C. (US); University of Texas Medical Branch, Galveston, TX (US).

REFERENCES

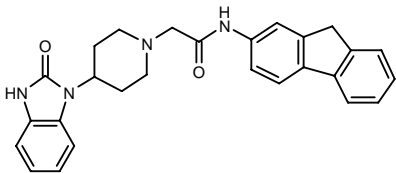
- 1. Kozikowski, A.P. et al. *Synthesis and biological properties of new 2β-alkyl- and 2β-aryl-3-(substituted phenyl)tropane derivatives: Stereochemical effect of C-3 on affinity and selectivity for neuronal dopamine and serotonin transporters*. J Med Chem 1998, 41(25): 4973.



Compound	R1	R2	R3	X	Formula
271247	NHMe	CONH2	COPh		C ₂₂ H ₂₆ N ₄ O ₃
271248	H	4-CN-PhCH2	COPh		C ₂₈ H ₂₇ N ₃ O ₂
271249	Ph	COEt	COPh		C ₂₉ H ₃₀ N ₂ O ₃
271250	Ph	COPr	C6H11		C ₂₉ H ₃₈ N ₂ O ₂
271251	Ph	Ac	COPh		C ₂₈ H ₂₈ N ₂ O ₃
271252	Ph	Ac	C6H11		C ₂₇ H ₃₄ N ₂ O ₂
271253	H	2-oxo-2,3-dihydro-1-benzimidazolyl	C6H11		C ₂₆ H ₃₂ N ₄ O ₂
271254	H	2-oxo-2,3-dihydro-1-benzimidazolyl	COPh	HCl	C ₂₇ H ₂₆ N ₄ O ₃ .HCl
271255	H	2-oxo-2,3-dihydro-1-benzimidazolyl	COCH2-Ph	HCl	C ₂₈ H ₂₈ N ₄ O ₃ .HCl
271257	Ph	CN	C6H11	HCl	C ₂₆ H ₃₁ N ₃ O.HCl
271258	CONH2	NHEt	C6H11	oxalate	C ₂₂ H ₃₄ N ₄ O ₂ .C ₂ H ₂ O ₄
271259	COEt	Ph	C6H11	HCl	C ₂₈ H ₃₆ N ₂ O ₂ .HCl



271256: C27 H24 N4 O3



271260: C27 H26 N4 O2

SOURCE – Bayer.

REFERENCES

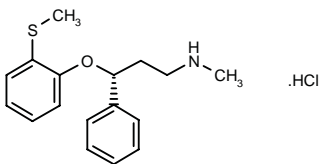
1. Connell, R.D. et al. (Bayer Corp.) *Amide derivs. as selective neuropeptide Y receptor antagonists*. WO 9835957.

LY-368975

270165

(R)-N-Methyl-3-[2-(methylsulfanyl)phenoxy]-3-phenyl-propylamine hydrochloride

(R)-Thionisoxetine



C17 H21 N O S . HCl; Mol wt: 323.8858

ACTION – A selective norepinephrine (NE) reuptake inhibitor ($K_i = 1.3$ nM) with improved potency and selectivity compared to tomoxetine and nisoxetine. *Ex vivo* in rats, it inhibited [³H]-NE uptake into hypothalamic synaptosomes with an ED₅₀ of 2.5 mg/kg p.o. and [³H]-tomoxetine binding to the NE transporter with an ED₅₀ of 2.7 mg/kg p.o. Compound prevented cardiac NE depletion induced in mice by 6-hydroxydopamine (ED₅₀ = 1.22 mg/kg p.o.). In 18-h food-deprived rats, compound at a dose of 10 mg/kg s.c. suppressed food intake until 4 h after reintroduction of food, and in nonfasted rats trained to drink sweetened condensed milk, it produced a significant dose-dependent decrease in consumption (44% at 3 mg/kg). No effect was observed on locomotor behavior in mice over the dose range 0.1-10 mg/kg p.o. Potentially useful in the treatment of obesity and eating disorders.

SOURCE – Lilly.

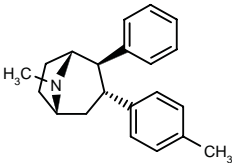
REFERENCES

1. Gehlert, D.R. et al. (Eli Lilly and Company) *N-Alkyl-3-phenyl-3-(2-alkyl-thiophenoxy)propylamines*. EP 591581.
2. Gehlert, D.R. et al. *The selective norepinephrine reuptake inhibitor, LY368975, reduces food consumption in animal models of feeding*. J Pharmacol Exp Ther 1998, 287(1): 122.

TREATMENT OF POISONING AND DRUG DEPENDENCY

270818

(1R,2R,3R,5S)-8-Methyl-3-(4-methylphenyl)-2-phenyl-8-azabicyclo[3.2.1]octane



C21 H25 N; Mol wt: 291.4355

ACTION – Cocaine analogue that adopts the boat conformation and exhibits high affinity for the dopamine transporter (DAT; $K_i = 2.87$ nM for displacement of [³H]-mazindol binding in rat striatal membranes) and high selectivity over the 5-HT transporter ($K_i = 173$ nM for displacement of [³H]-paroxetine binding in rat striatal membranes). It also potently inhibited dopamine uptake ($K_i = 4.16$ nM), showing much weaker activity against 5-HT uptake ($K_i = 287$ nM). It is currently undergoing studies in drug discrimination paradigms in animals.

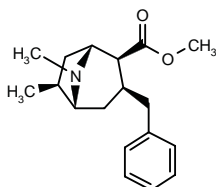
SOURCES – Georgetown University Medical Center, Washington, D.C. (US); University of Texas Medical Branch, Galveston, TX (US).

REFERENCES

1. Kozikowski, A.P. et al. *Synthesis and biological properties of new 2β-alkyl- and 2β-aryl-3-(substituted phenyl)tropane derivatives: Stereochemical effect of C-3 on affinity and selectivity for neuronal dopamine and serotonin transporters*. J Med Chem 1998, 41(25): 4973.

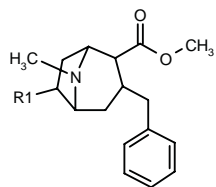
270936

(1*R*,2*S*,3*S*,5*R*,6*S*)-3-Benzyl-6,8-dimethyl-8-aza-bicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C18 H25 N O2; Mol wt: 287.4005

ACTION – Cocaine analogue for the treatment of cocaine addiction that binds to the cocaine binding site on the dopamine transporter (DAT; $K_i = 57 \pm 9$ nM for inhibition of [3 H]-Win-35428 in rat brain preparations) and is relatively resistant to metabolic degradation. Other specifically claimed compounds include the following:



Compound	R1	Isomer	Formula
270937	H	1 <i>R</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>S</i>	C ₁₇ H ₂₃ NO ₂
270938	Me	1 <i>R</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>R</i> ,6 <i>R</i>	C ₁₈ H ₂₅ NO ₂
270939	H	1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,5 <i>S</i>	C ₁₇ H ₂₃ NO ₂
270940	Me	1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i> ,6 <i>R</i>	C ₁₈ H ₂₅ NO ₂

SOURCE – Lousiana State University, Baton Rouge, LA (US).

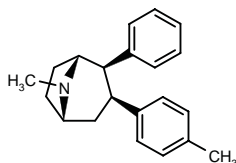
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RTI-422

271242

(1*R*,5*S*)-8-Methyl-3β-(4-methylphenyl)-2β-phenyl-8-azabicyclo[3.2.1]octane



C21 H25 N; Mol wt: 291.4355

ACTION – Potent and highly selective dopamine transporter (DAT) ligand ($IC_{50} = 1.96 \pm 0.08$ nM against [3 H]-Win-35428 binding) with much less activity at the 5-HT transporter ($IC_{50} = 11,000$ against [3 H]-paroxetine binding) and norepinephrine transporter ($IC_{50} = 479$ nM against [3 H]-nisoxetine binding). Such compounds may have potential in the treatment of cocaine abuse.

SOURCES – Emory University, Atlanta, GA (US); Research Triangle Institute, Research Triangle Park, NC (US).

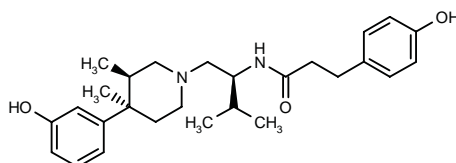
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RTI-5989-29

271481

3-(4-Hydroxyphenyl)-*N*-[1(*S*)-[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethylpiperidinylmethyl]-2-methylpropyl]-propionamide



C27 H38 N2 O3; Mol wt: 438.6082

Hydrochloride salt, m.p. 136-40 °C.

ACTION – Potent κ/μ -opioid receptor antagonist with high affinity for κ -receptors ($K_i = 6.91$ nM against [3 H]-U-69593 binding in guinea pig brain membranes) and significant affinity for μ -receptors ($K_i = 393$ nM against [3 H]-DAMGO binding in the same preparation), and high selectivity relative to δ -receptors ($K_i > 5700$ nM; $\delta/\kappa > 824$). Functional experiments evaluating its ability to inhibit agonist-stimulated [35 S]-GTP γ S binding in guinea pig caudate demonstrated pure antagonist activity against μ - ($K_i = 7.25$ nM) and κ -receptors ($K_i = 4.70$ nM), as well as its selectivity relative to δ -receptors ($K_i = 450$ nM). Potentially useful as a molecular probe and as a potential drug candidate for the treatment of heroin abuse.

SOURCES – Lilly; Research Triangle Institute, Research Triangle Park, NC (US); National Institute on Drug Abuse, Bethesda, MD (US).

REFERENCES

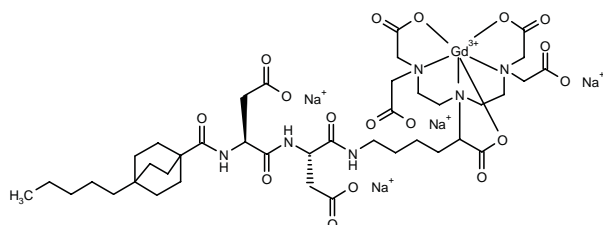
1. Thomas, J.B. et al. *Identification of an opioid kappa receptor subtype-selective N-substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine*. J Med Chem 1998, 41(26): 5188.

DIAGNOSTIC AGENTS

MP-2269

270808

Tetrasodium [6-[2-[bis(carboxylatomethyl)amino]ethyl]-7-carboxylato-3-(carboxylatomethyl)-12-[(4-pentyl-bicyclo[2.2.2]oct-1-ylcarbonyl)-L-aspartyl-L-aspartyl]-3,6,12-triazadodecanoato(7-)]gadolinolate



C40 H57 Gd Na4 N6 O17; Mol wt: 1143.1250

ACTION – Contrast agent for magnetic resonance (MR) angiography, a small-molecule, water-soluble, nonaromatic Gd³⁺ chelate that reversibly binds to blood proteins both *in vitro* and *in vivo*. In rabbits, compound at dose of 45 µmol/kg i.v. showed a long elimination half-life (> 2 h), ensuring an adequate imaging time frame. It was well tolerated in mice (LD₅₀ = 3 mmol/kg i.v.), and in MR imaging studies it showed excellent enhancement of blood vessel lumen at a relatively low dose (45 µmol/kg).

SOURCE – Mallinckrodt.

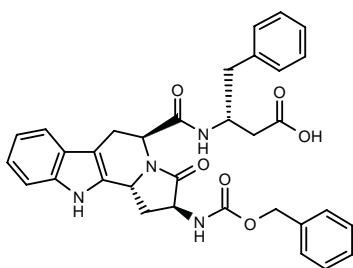
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1. Woulfe, S.R. (Mallinckrodt Medical Inc.) *Magnetic resonance blood pool agents*. WO 9820908.
2. Wallace, R.A. et al. *Synthesis and preliminary evaluation of MP-2269: A novel, nonaromatic small-molecule blood-pool MR contrast agent*. Magn Reson Med 1998, 40(5): 733.

PHARMACOLOGICAL TOOLS

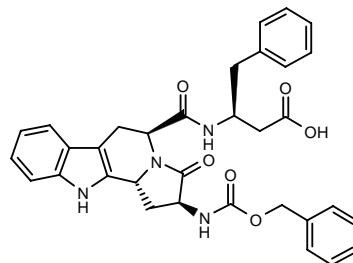
271390

3(*R*)-[(2*S*,5*S*,11*bR*)-2-(Benzyloxycarbamoyl)-3-oxo-2,3,5,6,11,11*b*-hexahydro-1*H*-indolizino[8,7-*b*]indol-5-ylcarbonyl]-4-phenylbutyric acid



C33 H32 N4 O6; Mol wt: 580.6378

ACTION – Cholecystokinin CCK₁ (CCK_A) receptor antagonist giving an IC₅₀ of 88 nM for inhibition of [³H]-propionyl-CCK-8 binding in rat pancreas, with high selectivity over CCK₂ (CCK_B) receptors (IC₅₀ >10,000 nM against [³H]-propionyl-CCK-8 binding in rat cortical membranes). In functional assays, compound at a concentration of 10 µM inhibited CCK-8-induced contractions in guinea pig ileum longitudinal muscle myenteric plexus by 72%. Another compound from this series of highly constrained dipeptoid analogues is:



271389: C33 H32 N4 O6

SOURCES – CSIC, Madrid (ES); Universidad de Navarra, Pamplona (ES).

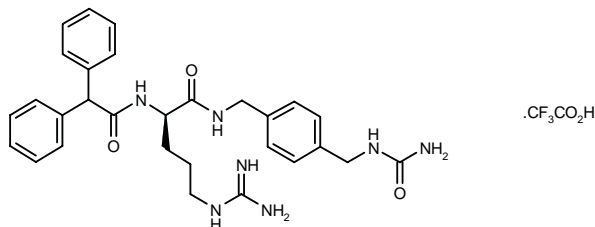
REFERENCES

1. de la Figuera, N. et al. *Highly constrained dipeptoid analogues containing a type II' β-turn mimic as novel and selective CCK-A receptor ligands*. Bioorg Med Chem Lett 1999, 9(1): 43.

BIBO-3304*

252987

N^α-(2,2-Diphenylacetyl)-D-arginine 4-(ureidomethyl)benzylamide trifluoroacetate



C29 H35 N7 O3 . C2 H F3 O2; Mol wt: 643.6720

ACTION – Nonpeptide neuropeptide Y (NPY) antagonist with selectivity for Y₁ receptors (IC₅₀ = 0.38 and 0.72 nM, respectively, for human and rat Y₁ receptors) and low affinity for human Y₂, human and rat Y₄ and human and rat Y₅ receptors (IC₅₀ > 1000 nM). When administered into the paraventricular nucleus of rats at a dose of 30 µg, it inhibited the feeding response induced by NPY, as well as hyperphagia induced by a 24-h fast. Potentially useful as a tool for studying the physiological role of the Y₁ receptor.

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Engel, W. et al. (Dr. Karl Thomae GmbH) *Amino acid derivs., pharmaceutical compns. containing these cpds. and processes for preparing them*. DE 19544687, EP 885186, WO 9719911.
2. Wieland, H.A. et al. *Subtype selectivity of the novel nonpeptide neuropeptide Y Y1 receptor antagonist BIBO 3304 and its effect on feeding in rodents*. Br J Pharmacol 1998, 125(3): 549.

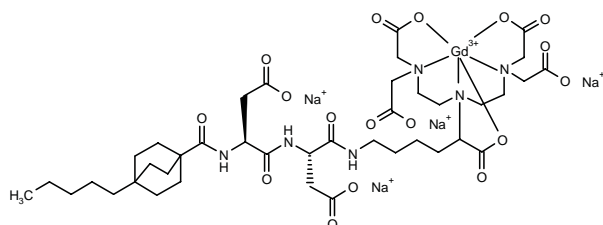
*Identified compound **252987** Drug Data Report 1997, 019(09): 0797.

DIAGNOSTIC AGENTS

MP-2269

270808

Tetrasodium [6-[2-[bis(carboxylatomethyl)amino]ethyl]-7-carboxylato-3-(carboxylatomethyl)-12-[(4-pentyl-bicyclo[2.2.2]oct-1-ylcarbonyl)-L-aspartyl-L-aspartyl]-3,6,12-triazadodecanoato(7-)]gadolinolate



C40 H57 Gd Na4 N6 O17; Mol wt: 1143.1250

ACTION – Contrast agent for magnetic resonance (MR) angiography, a small-molecule, water-soluble, nonaromatic Gd³⁺ chelate that reversibly binds to blood proteins both *in vitro* and *in vivo*. In rabbits, compound at dose of 45 µmol/kg i.v. showed a long elimination half-life (> 2 h), ensuring an adequate imaging time frame. It was well tolerated in mice (LD₅₀ = 3 mmol/kg i.v.), and in MR imaging studies it showed excellent enhancement of blood vessel lumen at a relatively low dose (45 µmol/kg).

SOURCE – Mallinckrodt.

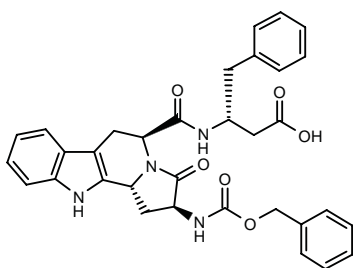
REFERENCES

1. Woulfe, S.R. (Mallinckrodt Medical Inc.) *Magnetic resonance blood pool agents*. WO 9820908.
2. Wallace, R.A. et al. *Synthesis and preliminary evaluation of MP-2269: A novel, nonaromatic small-molecule blood-pool MR contrast agent*. Magn Reson Med 1998, 40(5): 733.

PHARMACOLOGICAL TOOLS

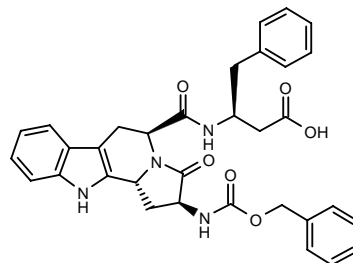
271390

3(*R*)-[(2*S*,5*S*,11*bR*)-2-(Benzyloxycarbamoyl)-3-oxo-2,3,5,6,11,11*b*-hexahydro-1*H*-indolizino[8,7-*b*]indol-5-ylcarbonyl]-4-phenylbutyric acid



C33 H32 N4 O6; Mol wt: 580.6378

ACTION – Cholecystokinin CCK₁ (CCK_A) receptor antagonist giving an IC₅₀ of 88 nM for inhibition of [³H]-propionyl-CCK-8 binding in rat pancreas, with high selectivity over CCK₂ (CCK_B) receptors (IC₅₀ >10,000 nM against [³H]-propionyl-CCK-8 binding in rat cortical membranes). In functional assays, compound at a concentration of 10 µM inhibited CCK-8-induced contractions in guinea pig ileum longitudinal muscle myenteric plexus by 72%. Another compound from this series of highly constrained dipeptoid analogues is:



271389: C33 H32 N4 O6

SOURCES – CSIC, Madrid (ES); Universidad de Navarra, Pamplona (ES).

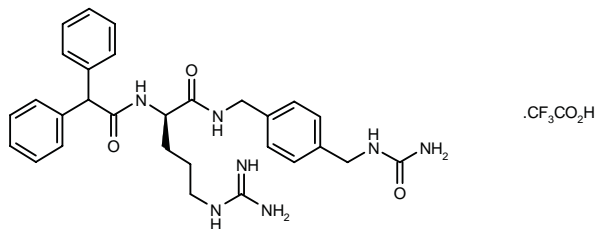
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1. de la Figuera, N. et al. *Highly constrained dipeptoid analogues containing a type II' β-turn mimic as novel and selective CCK-A receptor ligands*. Bioorg Med Chem Lett 1999, 9(1): 43.

BIBO-3304*

252987

N^α-(2,2-Diphenylacetyl)-D-arginine 4-(ureidomethyl)benzylamide trifluoroacetate



C29 H35 N7 O3 . C2 H F3 O2; Mol wt: 643.6720

ACTION – Nonpeptide neuropeptide Y (NPY) antagonist with selectivity for Y₁ receptors (IC₅₀ = 0.38 and 0.72 nM, respectively, for human and rat Y₁ receptors) and low affinity for human Y₂, human and rat Y₄ and human and rat Y₅ receptors (IC₅₀ > 1000 nM). When administered into the paraventricular nucleus of rats at a dose of 30 µg, it inhibited the feeding response induced by NPY, as well as hyperphagia induced by a 24-h fast. Potentially useful as a tool for studying the physiological role of the Y₁ receptor.

SOURCE – Boehringer Ingelheim.

REFERENCES

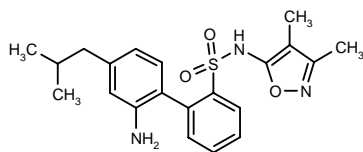
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2. Wieland, H.A. et al. *Subtype selectivity of the novel nonpeptide neuropeptide Y Y1 receptor antagonist BIBO 3304 and its effect on feeding in rodents*. Br J Pharmacol 1998, 125(3): 549.

*Identified compound **252987** Drug Data Report 1997, 019(09): 0797.

BMS-187308

271483

2'-Amino-N-(3,4-dimethyl-5-isoxazolyl)-4'-isobutyl[1,1'-biphenyl]-2-sulfonamide



C21 H25 N3 O3 S; Mol wt: 399.5125

ACTION – Endothelin antagonist with high affinity for the ET_A subtype ($K_i = 4.7$ nM) and selectivity over the ET_B subtype ($K_i = 1.7$ μ M). However, in functional assays it showed little selectivity, inhibiting ET-1-induced rabbit carotid artery contractions (ET_A -mediated effect) with a K_B value of 0.12 μ M and blocking sarafotoxin S6c-induced relaxation of phenylephrine-contracted rat aorta (ET_B -mediated effect) with a K_B value of 0.64 μ M. It exhibited good and long-lasting inhibition of the pressor effect produced by ET-1 ($60 \pm 4\%$ inhibition at 3 h after an oral dose of 30 μ mol/kg) or big ET-1 infusion ($49 \pm 5\%$ inhibition after an i.v. dose of 3 μ mol/kg) in conscious, normotensive rats. It was also able to attenuate the ET-1-induced pressor response in conscious monkeys at doses of 10 and 30 μ mol/kg i.v. Oral bioavailability in rats was 48% and compound was rapidly absorbed. Potentially useful as a pharmacological tool for investigating the role of endothelin in various disease models.

SOURCE – Bristol-Myers Squibb.

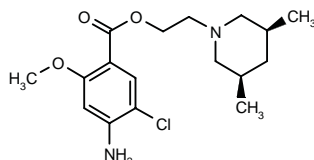
REFERENCES

1. Murugesan, N. and Hunt, J.T. (Bristol-Myers Squibb Co.) *Phenyl sulfonamide and their use as endothelin antagonists*. EP 569193, JP 94049046, US 5514696.
2. Murugesan, N. et al. *Biphenylsulfonamide endothelin antagonists: Structure-activity relationships of a series of mono- and disubstituted analogues and pharmacology of the orally active endothelin antagonist 2'-amino-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide (BMS-187308)*. J Med Chem 1998, 41(26): 5198.

ML-10375*

237381

cis-4-Amino-2-methoxy-5-chlorobenzoic acid 2-(3,5-dimethylpiperidin-1-yl)ethyl ester



C17 H25 Cl N2 O3; Mol wt: 340.8485

M.p. 115 °C.

ACTION – High-affinity, competitive 5-HT₄ receptor antagonist, as shown in binding studies by a K_i of 0.26 nM against [³H]-GR-113808 in rat striatal membranes, and in functional assays by inhibition of 5-HT-mediated contractions in guinea pig ileum ($IC_{50} = 11$ nM) and by blockade of 5-HT-induced relaxation in rat esophagus muscle ($pA_2 = 8.6$). Compound also acted as an inverse agonist at the human 5-HT_{4(c)} receptor.

SOURCE – Sanofi.

REFERENCES

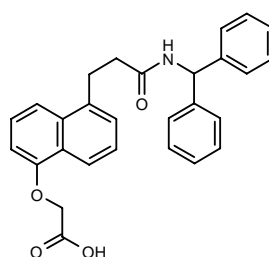
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2. Blondel, O. et al. *The 5-HT₄ receptor antagonist ML10375 inhibits the constitutive activity of human 5-HT_{4(c)} receptor*. Br J Pharmacol 1998, 125(4): 595.
3. Yang, D. et al. *New esters of 4-amino-5-chloro-2-methoxybenzoic acid as potent agonists and antagonists for 5-HT₄ receptors*. J Med Chem 1997, 40(4): 608.

*Identified compound **237381** (see **234573**) Drug Data Report 1996, 018(07): 0625.

ONO-AP-324*

238890

2-[5-[2-[N-(Diphenylmethyl)carbamoyl]ethyl]naphthalen-1-yloxy]acetic acid



C28 H25 N O4; Mol wt: 439.5085

ACTION – Potent nonprostanoid EP₃ receptor partial agonist ($K_i = 11$ nM for mouse EP_{3 α} receptor) with high selectivity over EP₂, EP₄ and FP receptors (mouse) and IP and TP receptors (human; $K_i > 10$ μ M), as well as the EP₁ receptor (mouse; $K_i = 4.6$ μ M). It behaved as a partial agonist in isolated guinea pig aorta, but as a full agonist in the field-stimulated guinea pig vas deferens. Potentially useful as a pharmacological tool for elucidating the physiological role of the EP₃ receptor.

SOURCE – Ono.

REFERENCES

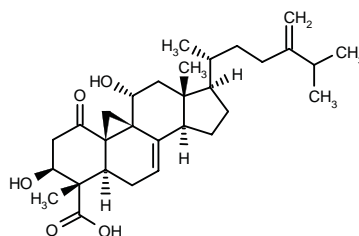
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2. Jones, R.L. et al. *Characterization of a prostanoid EP₃-receptor in guinea-pig aorta: Partial agonist action of the non-prostanoid ONO-AP-324*. Br J Pharmacol 1998, 125(6): 1288.

*Identified compound **238890** Drug Data Report 1996, 018(10): 0863.

S-19159

269608

(3 β ,4 α ,5 α ,9 β ,11 α ,17 β)-3,11-Dihydroxy-4,9-dimethyl-9,19-methano-24-methylene-1-oxocholestan-7-en-4-carboxylic acid



C30 H44 O5; Mol wt: 484.6726

Colorless needles, m.p. > 196 °C (decomp.).

ACTION – Modulator of neurite outgrowth isolated from the fermentation broth of the fungus *Preussia aemulans*. In rat embryonic cerebral cortical neurons, compound reduced the number of neurites at concentrations of 0.1–10 nM and a similar effect was observed in rat hippocampal and cerebellar neurons, but not in rat pheochromocytoma PC12-22a cells or rat dorsal root neurons, indicating specificity for neurons derived from the CNS. Potentially useful as a pharmacological tool for elucidating the mechanism of neurite outgrowth.

SOURCE – Kyowa Hakko.

REFERENCES

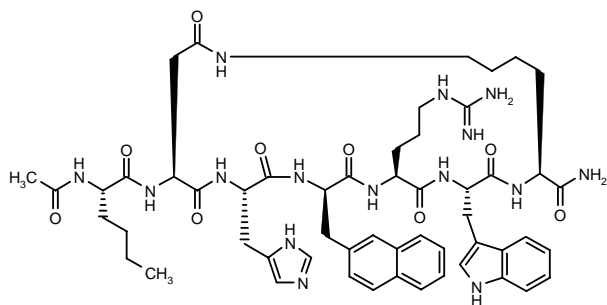
1. Sato, T. et al. *S19159, a modulator of neurite outgrowth produced by the ascomycete *Preussia aemulans*. I. Producing strain, fermentation, isolation and biological activity.* J Antibiot 1998, 51(10): 897.
2. Sato, T. et al. *S19159, a modulator of neurite outgrowth produced by the ascomycete *Preussia aemulans*. II. Structure elucidation.* J Antibiot 1998, 51(11): 1047.

SHU-9119

269782

N-Acetyl-L-norleucyl-L-aspartyl-L-histidyl-3-(2-naphthyl)-D-alanyl-L-arginyl-L-tryptophyl-L-lysineamide cyclic C-4.2-N-6.7-amide

MBX-36



C54 H71 N15 O9; Mol wt: 1074.2510

White powder.

ACTION – Cyclic lactam α -melanotropin analogue with potent antagonist activity at neuronal melanocortin (MC) receptor subtypes MC3 and MC4 (pA_2 = 8.3 and 9.3, respectively) and full agonist activity at subtypes MC1 (EC_{50} = 0.036 nM using human receptor) and MC5 (EC_{50} = 434 nM using mouse receptor). Potentially useful as a pharmacological tool to determine the physiological role of melanocortin receptors.

SOURCES – University of Arizona, Tucson, AZ (US); Oregon Health Sciences University, Portland, OR (US).

REFERENCES

1. Fan, W. et al. *Role of melanocortinergic neurons in feeding and the agouti obesity syndrome.* Nature 1997, 385(6612): 165.
2. Getting, S.J. et al. *Agonism at melanocortin receptor type 3 on macrophages inhibits neutrophil influx.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst A5.
3. Hruby, V.J. et al. *Cyclic lactam α -melanotropin analogues of Ac-Nle⁴-cyclo[Asp⁶, D-Phe⁷, Lys¹⁰] α -melanocyte-stimulating hormone-(4-10)-NH₂ with bulky aromatic amino acids at position 7 show high antagonist potency and selectivity at specific melanocortin receptors.* J Med Chem 1995, 38(18): 3454.
4. Huang, Q.-H. et al. *Antipyretic role of endogenous melanocortins mediated by central melanocortin receptors during endotoxin-induced fever.* J Neurosci 1997, 17(9): 3343.
5. Rossi, M. et al. *A C-terminal fragment of Agouti-related protein increases feeding and antagonizes the effect of α -melanocyte stimulating hormone in vivo.* Endocrinology 1998, 139(10): 4428.
6. Schaaper, W.M.M. et al. *Synthesis of cyclic α -MSH peptides.* Lett Pept Sci 1998, 5(2-3): 205.
7. Schioth, H.B. et al. *Discovery of novel melanocortin₄ receptor selective MSH analogues.* Br J Pharmacol 1998, 124(1): 75.
8. Schioth, H.B. et al. *Selectivity of cyclic [D-Nal¹⁷] and [D-Phe⁷] substituted MSH analogs for the melanocortin receptor subtypes.* Peptides 1997, 18(7): 1009.

PHARMACEUTICAL AIDS

271457

Mixed-backbone oligonucleotide containing phosphodiester (o) and phosphorothioate (s) linkages and a 9-deoxynucleoside segment in the center flanked by 5 and 2'-O-methylribose nucleosides at both the 3' and 5'-ends, whose sequence is:

5'-GsCoGsUoGsCsCsTsCsCsTsCsAsCoUsGoGsC-3'

ACTION – Second-generation antisense mixed-backbone oligonucleotide with similar antisense properties and tissue distribution compared to the parent phosphorothioate oligonucleotide but reduced phosphorothioate oligonucleotide-related side effects such as prolongation of APTT (activated partial thromboplastin time). Further studies are in progress to assess its therapeutic potential.

SOURCE – Hybridon.

REFERENCES

1. Zhou, W. and Agrawal, S. *Mixed-backbone oligonucleotides as second-generation antisense agents with reduced phosphorothioate-related side effects.* Bioorg Med Chem Lett 1998, 8(22): 3269.

Colorless needles, m.p. > 196 °C (decomp.).

ACTION – Modulator of neurite outgrowth isolated from the fermentation broth of the fungus *Preussia aemulans*. In rat embryonic cerebral cortical neurons, compound reduced the number of neurites at concentrations of 0.1–10 nM and a similar effect was observed in rat hippocampal and cerebellar neurons, but not in rat pheochromocytoma PC12-22a cells or rat dorsal root neurons, indicating specificity for neurons derived from the CNS. Potentially useful as a pharmacological tool for elucidating the mechanism of neurite outgrowth.

SOURCE – Kyowa Hakko.

REFERENCES

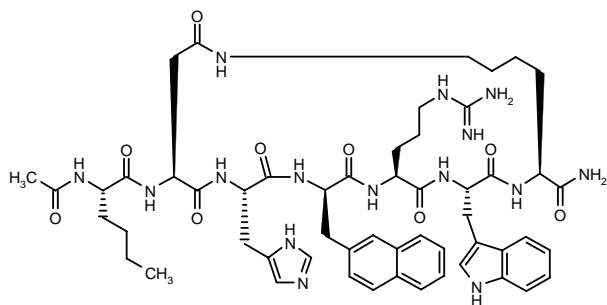
1. Sato, T. et al. *S19159, a modulator of neurite outgrowth produced by the ascomycete *Preussia aemulans*. I. Producing strain, fermentation, isolation and biological activity.* J Antibiot 1998, 51(10): 897.
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SHU-9119

269782

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MBX-36



C54 H71 N15 O9; Mol wt: 1074.2510

White powder.

ACTION – Cyclic lactam α -melanotropin analogue with potent antagonist activity at neuronal melanocortin (MC) receptor subtypes MC3 and MC4 ($pA_2 = 8.3$ and 9.3 , respectively) and full agonist activity at subtypes MC1 ($EC_{50} = 0.036$ nM using human receptor) and MC5 ($EC_{50} = 434$ nM using mouse receptor). Potentially useful as a pharmacological tool to determine the physiological role of melanocortin receptors.

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2. Getting, S.J. et al. *Agonism at melanocortin receptor type 3 on macrophages inhibits neutrophil influx.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst A5.
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4. Huang, Q.-H. et al. *Antipyretic role of endogenous melanocortins mediated by central melanocortin receptors during endotoxin-induced fever.* J Neurosci 1997, 17(9): 3343.
5. Rossi, M. et al. *A C-terminal fragment of Agouti-related protein increases feeding and antagonizes the effect of α -melanocyte stimulating hormone in vivo.* Endocrinology 1998, 139(10): 4428.
6. Schaaper, W.M.M. et al. *Synthesis of cyclic α -MSH peptides.* Lett Pept Sci 1998, 5(2-3): 205.
7. Schioth, H.B. et al. *Discovery of novel melanocortin₄ receptor selective MSH analogues.* Br J Pharmacol 1998, 124(1): 75.
8. Schioth, H.B. et al. *Selectivity of cyclic [D-Nal¹⁷] and [D-Phe⁷] substituted MSH analogs for the melanocortin receptor subtypes.* Peptides 1997, 18(7): 1009.

PHARMACEUTICAL AIDS

271457

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ACTION – Second-generation antisense mixed-backbone oligonucleotide with similar antisense properties and tissue distribution compared to the parent phosphorothioate oligonucleotide but reduced phosphorothioate oligonucleotide-related side effects such as prolongation of APTT (activated partial thromboplastin time). Further studies are in progress to assess its therapeutic potential.

SOURCE – Hybridon.

REFERENCES

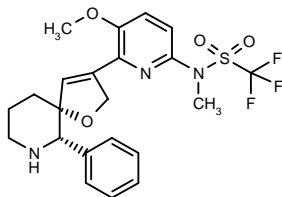
1. Zhou, W. and Agrawal, S. *Mixed-backbone oligonucleotides as second-generation antisense agents with reduced phosphorothioate-related side effects.* Bioorg Med Chem Lett 1998, 8(22): 3269.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

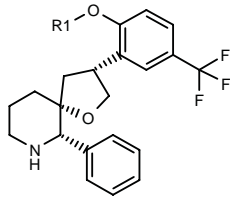
271894

N-[5-Methoxy-6-[(5*R*,6*S*)-6-phenyl-1-oxa-7-azaspiro-[4.5]dec-3-en-3-yl]pyridin-2-yl]-*N*-methyltrifluoromethanesulfonamide

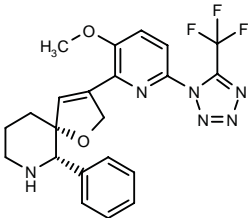


C22 H24 F3 N3 O4 S; Mol wt: 483.5086

ACTION – Agent for the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia, a potent tachykinin, especially substance P (NK₁ receptor), antagonist. Within this series of specifically claimed spiro-azacyclic derivatives, the following are also included:



Compound	R1	Formula
271896	Me	C ₂₁ H ₂₃ F ₃ N ₂ O ₂
271898	CHF2	C ₂₁ H ₂₁ F ₅ N ₂ O ₂
271899	cyclopropyl	C ₂₃ H ₂₅ F ₃ N ₂ O ₂



271895: C22 H21 F3 N6 O2

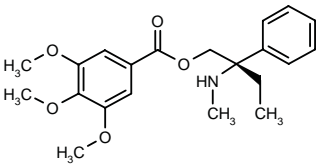
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Kulagowski, J.J. et al. (Merck Sharp & Dohme Ltd.) *Spiro-azacyclic derivs. and their use as therapeutic agents*. WO 9854187.

272195

3,4,5-Trimethoxybenzoic acid 2(*S*)-(methylamino)-2-phenylbutyl ester



C21 H27 N O5; Mol wt: 373.4463

ACTION – Agent for the treatment of chronic pain, for example pain of osteoarthritis, polyarthritis, postsurgical pain, polyneuropathy and in vascular conditions such as arteritis and varicose ulcer, the (*S*)-isomer of *N*-demethyltrimebutine (NDTMB), a metabolite of the spasmolytic agent trimebutine (TMB); the (*S*)-isomer has been found to show equal or greater analgesic properties *in vivo* compared to racemic or (*R*)-NDTMB, while exhibiting lower affinity for opiate receptors than racemic or (*R*)-NDTMB and racemic TMB, and thus lacking opiate side effects. Compound exhibited K_i values of 221, 2456 and 1053 nM for μ-, δ- and κ-opioid receptors, respectively, compared to K_i values of 82, 735 and 405 nM, respectively, for the (*R*)-isomer, 152, 943 and 491 nM, respectively, for racemic NDTMB and 123, 302 and 145 nM, respectively, for racemic TMB. In the formaldehyde test in mice, compound exhibited comparable analgesic activity to racemic NDTMB and superior activity to the (*R*)-isomer at 20 mg/kg s.c.; contrary to racemic and (*R*)-NDTMB, its activity was only partially inhibited by naloxone, suggesting that it acts by a nonopiate mechanism. Compound also showed analgesic activity in several models of chronic pain and appears to be devoid of addictive potential, in contrast to the (*R*)-isomer.

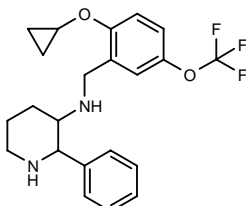
SOURCE – Jouveinal.

REFERENCES

1. Dahl, S.G. et al. (Jouveinal SA) (S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate, its application to the treatment of chronic pain. WO 9901417.

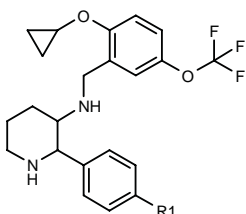
272202

N-[2-(Cyclopropoxy)-5-(trifluoromethoxy)benzyl]-*N*-(2-phenylpiperidin-3-yl)amine



C22 H25 F3 N2 O2; Mol wt: 406.4455

ACTION – Potent tachykinin, particularly NK₁ (IC₅₀ = 0.17 nM), receptor antagonist reported to possess high hepatic stability and oral bioavailability. Potentially useful for the treatment or prevention of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other specifically claimed compounds from this series of substituted 3-(benzylamino)piperidine derivatives include the following:



Compound	R1	Isomer	Formula
272203	H	2S,3S	C ₂₂ H ₂₅ F ₃ N ₂ O ₂
272204	F		C ₂₂ H ₂₄ F ₄ N ₂ O ₂

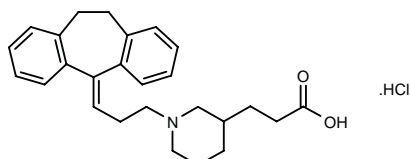
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Elliott, J.M. (Merck Sharp & Dohme Ltd.) Subst. 3-(benzylamino)piperidine derivs. and their use as therapeutic agents. WO 9900368.

272236

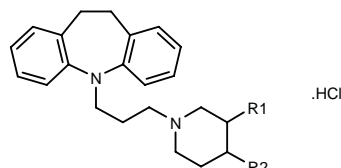
3-[1-[3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)propyl]-3-piperidinyl]propionic acid hydrochloride



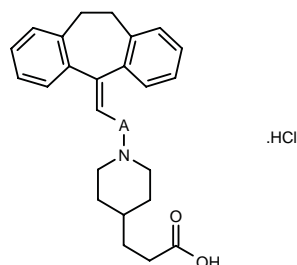
C26 H31 N O2 . HCl; Mol wt: 425.9968

ACTION – Agent for the treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibers play a role such as neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis that

acts by inhibiting the release of neuropeptides from peripheral and central endings of sensory C-fibers. Compound also inhibits the release of insulin-antagonizing peptides such as CGRP and amylin from peripheral nerve endings and is thus expected to be useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) and age-associated obesity. *In vivo*, compound was shown to inhibit histamine-induced paw edema in rats (22% inhibition at 1.0 mg/kg i.p.) and histamine-induced hyperglycemia in mice (42% inhibition at 1.0 mg/kg i.p.). It is also reported to improve the glucose tolerance in diabetic *ob/ob* mice following oral administration. Within this series of tricyclic compounds, the following are also specifically claimed:



Compound	R1	R2	Formula
272237	CH ₂ CH ₂ CO ₂ H	H	C ₂₅ H ₃₂ N ₂ O ₂ ·HCl
272240	H	CH ₂ CH ₂ CO ₂ H	C ₂₅ H ₃₂ N ₂ O ₂ ·HCl



Compound	A	Formula
272238	-CH ₂ -	C ₂₅ H ₂₉ NO ₂ ·HCl
272239	-(CH ₂) ₂ -	C ₂₆ H ₃₁ NO ₂ ·HCl

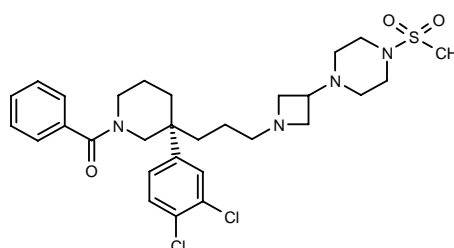
SOURCE – Novo Nordisk.

REFERENCES

1. Andersen, K.E. et al. (Novo Nordisk A/S) Novel heterocyclic cpds. WO 9900367.

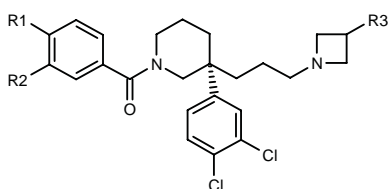
272352

(+)-1-[3(*R*)-(3,4-Dichlorophenyl)-3-[3-[4-(methylsulfonyl)-1-piperazinyl]-1-azetidyl]propyl]piperidinyl]-1-(phenyl)methanone



C29 H38 Cl2 N4 O3 S; Mol wt: 593.6162

ACTION – Tachykinin antagonist with affinity for NK₁, NK₂ and/or NK₃ receptors (pIC₅₀ = 8.8 against [³H]-senktide binding to NK₃ receptors in guinea pig cortex), claimed for the treatment or prevention of inflammatory disorders such as asthma, arthritis and psoriasis, CNS disorders such as anxiety, depression, dementia and psychosis, gastrointestinal disorders such as functional bowel disease, irritable bowel syndrome, gastroesophageal reflux, fecal incontinence, colitis or Crohn's disease, urogenital tract disorders such as incontinence and cystitis, chronic obstructive airways disease, allergy, diabetic neuropathy, neuralgia, cancer, migraine and acute or chronic pain. A representative compound from a series of azetidinypropylpiperidines, wherein the following are also included:



Compound	R1=R2	R3	Formula
272353	H	N(Ph)SO ₂ Me	C ₃₁ H ₃₆ Cl ₂ N ₃ O ₃ S
272354	F	4-(MeSO ₂)-1-Piz	C ₂₉ H ₃₆ Cl ₂ F ₂ N ₄ O ₃ S

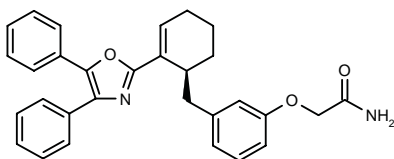
SOURCE – Pfizer.

REFERENCES

1. Alker, D. et al. (Pfizer Ltd.;Pfizer Inc.) *Azetidinypropylpiperidine derivs., intermediates and use as tachykinin antagonists*. WO 9901451.

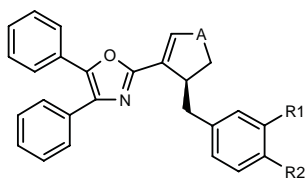
272903

2-[3-[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1(S)-ylmethyl]phenoxy]acetamide



C₃₀ H₂₈ N₂ O₃; Mol wt: 464.5622

ACTION – Agent for the treatment of pain, inflammation, autoimmune and immune diseases, thrombosis, cancer and neurodegenerative disorders that displays strong binding affinity for EP₄ receptors (> 80% inhibition of [³H]-PGE₂ binding to human receptors expressed in COS-7 cells at 10 μM). In addition, it was shown to inhibit PGE₂-induced IgE secretion in murine B-lymphocytes at 10 μM. Other compounds from this series of oxazole derivatives include the following:



Compound	R1	R2	A	Formula
272904	OMe	H	-CH ₂ -	C ₂₈ H ₂₅ NO ₂
272905	H	CO ₂ H	-(CH ₂) ₂ -	C ₂₉ H ₂₅ NO ₃

SOURCE – Fujisawa.

REFERENCES

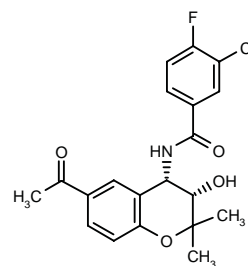
1. Hattori, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Oxazole cpds. useful as PGE₂ agonists and antagonists*. WO 9855468.

ANTIMIGRAINE DRUGS

SB-220453*

231735

(3*S*,4*S*)-*cis*-*N*-(6-Acetyl-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-3-chloro-4-fluorobenzamide



C₂₀ H₁₉ Cl F N O₄; Mol wt: 391.8300

ACTION – Potential antimigraine agent, an analogue of the antiepileptic compound SB-204269 that acts via a novel mechanism, interacting with a unique binding site in brain labeled by [³H]-SB-204269. Compound significantly increased seizure threshold in the rat maximal electroshock seizure (MES) model at a dose of 3 mg/kg p.o., indicating high efficacy at moderating abnormally high levels of neuronal excitability, and it inhibited neurogenic plasma extravasation in the dura mater, with activity comparable to sumatriptan; at 10 mg/kg i.p. it produced a complete block of neurogenic extravasation. Antagonism of cortical spreading depression has also been reported. SB-220453 is devoid of cardiovascular side effects and behavioral depressant effects at doses of 50-200 mg/kg p.o.

SOURCE – SmithKline Beecham.

REFERENCES

1. Chan, W.N. et al. (SmithKline Beecham plc) *Benzopyrans and their use as therapeutic agents*. EP 764157, JP 98501251, US 5760074, WO 9534545.
2. Chan, W.N. et al. *Identification of (-)-cis-6-acetyl-4*S*-(3-chloro-4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2*H*-benzo[b]pyran-3*S*-ol as a potential antimigraine agent*. Bioorg Med Chem Lett 1999, 9(2): 285.
3. SmithKline Beecham to file 13 new chemical entities and 8 vaccines over the next 3 years. SmithKline Beecham Press Release 1995, Sept 27.
4. SmithKline Beecham Annual Report 1995.

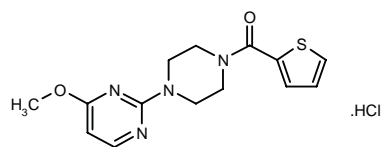
*Identified compound **231735** Drug Data Report 1996, 018(04): 0317.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

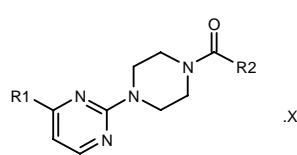
272982

1-[4-(4-Methoxy-2-pyrimidinyl)-1-piperazinyl]-1-(2-thienyl)methanone hydrochloride



C14 H16 N4 O2 S . HCl; Mol wt: 340.8333

ACTION – Agent with sedative, anticonvulsant, hypnotic and general anesthetic effects. Hypnotic activity was tested by its ability to potentiate barbital-induced hypnosis in mice (ED₅₀ = 8.7 mg/kg i.p.; ED₅₀ meprobamate = 84.5 mg/kg i.p.). General anesthetic activity was assessed in mice by measuring start and duration of sleep time; at 80 mg/kg i.v. it produced immediate anesthesia, which lasted for 5.3 min, being more potent than propofol and having a faster onset of action. Sedative activity was assessed by measuring motor activity in mice; compound was found to decrease motor activity in a dose-dependent manner upon i.p. administration, being more potent than pentobarbital and melatonin. In addition, it exhibited analgesic activity in the phenylbenzoquinone-induced writhing test in mice (ED₅₀ = 48 and 72 mg/kg s.c. and p.o., respectively, vs. 84 and 120 mg/kg s.c. and p.o., respectively, for aspirin). A representative compound from a series of acylpiperazinylpyrimidines, wherein the following are also included:



Compound	R1	R2	X	Formula
272983	OMe	2-furyl	HCl	C ₁₄ H ₁₆ N ₄ O ₃ .HCl
272985	OMe	Ph	HCl	C ₁₆ H ₁₈ N ₄ O ₂ .HCl
272986	OMe	2-CF ₃ -Ph	HCl	C ₁₇ H ₁₇ F ₃ N ₄ O ₂ .HCl
272987	CF ₃	3-Pyr	HCl	C ₁₅ H ₁₄ F ₃ N ₅ O.HCl
272988	OMe	2-Pyr	2HCl	C ₁₅ H ₁₇ N ₅ O ₂ .2HCl
272989	OEt	2-thienyl	HCl	C ₁₅ H ₁₈ N ₄ O ₂ S.HCl
272990	OEt	3-Cl-2-thienyl	HCl	C ₁₅ H ₁₇ ClN ₄ O ₂ S.HCl
272991	OEt	2-CF ₃ -Ph	HCl	C ₁₈ H ₁₉ F ₃ N ₄ O ₂ .HCl
272992	i-PrO	4-F-Ph	HCl	C ₁₈ H ₂₁ FN ₄ O ₂ .HCl
272993	OMe	2-thiazolyl		C ₁₃ H ₁₅ N ₅ O ₂ S
272994	OMe	3-F-2-thienyl	HCl	C ₁₄ H ₁₅ FN ₄ O ₂ S.HCl

SOURCE – Esteve.

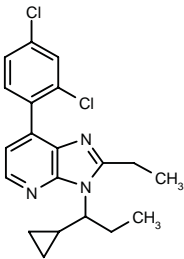
REFERENCES

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ANXIOLYTICS

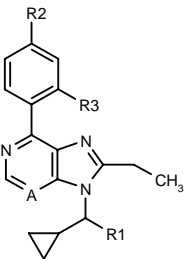
272336

3-(1-Cyclopropylpropyl)-7-(2,4-dichlorophenyl)-2-ethyl-3H-imidazo[4,5-b]pyridine



C20 H21 Cl2 N3; Mol wt: 374.3129

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist claimed for the treatment of affective disorder, anxiety, depression, posttraumatic stress disorder, supranuclear palsy, epilepsy, stroke, irritable bowel syndrome, immune suppression, Alzheimer’s disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, cardiovascular disorders, obesity or fertility disorders. Other compounds from this series of imidazopyrimidines and imidazopyridines include the following:



Compound	R1	R2=R3	A	Formula
272337	Et	Cl	CH	C ₂₀ H ₂₁ Cl ₂ N ₃
272338	cyclopropyl	CF ₃	N	C ₂₂ H ₂₀ F ₆ N ₄

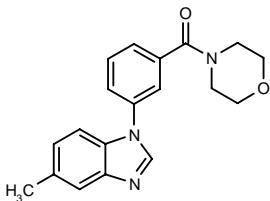
SOURCE – DuPont Pharmaceuticals.

REFERENCES

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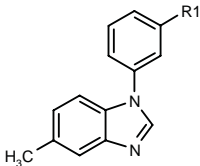
273211

1-[3-(5-Methyl-1*H*-benzimidazol-1-yl)phenyl]-1-(4-morpholinyl)methanone



C19 H19 N3 O2; Mol wt: 321.3781

ACTION – Anxiolytic agent and anticonvulsant, a GABA_A receptor agonist with selective affinity for the α2 and/or α3 subunits relative to the α1 subunit, and therefore expected to be associated with a reduced propensity to cause sedation. Other specifically claimed compounds from this series of phenylbenzimidazole derivatives include the following:



Compound	R1	Formula
273212	CON(Et)2	C ₁₉ H ₂₁ N ₃ O
273213	4-Pyr-CH2NHCO	C ₂₁ H ₁₈ N ₄ O
273214	2-Pyr-CH2NHCO	C ₂₁ H ₁₈ N ₄ O
273215	4-thiomorpholinyl-CO	C ₁₉ H ₁₈ N ₃ OS
273216	4-OH-1-Pip-CO	C ₂₀ H ₂₁ N ₃ O ₂
273217	4-morpholinyl-CH2	C ₁₉ H ₂₁ N ₃ O

SOURCE – Merck Sharp & Dohme.

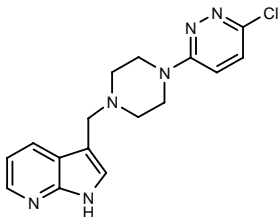
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ANTIPSYCHOTIC DRUGS

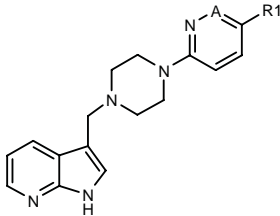
272413

3-[4-(6-Chloro-3-pyridazinyl)-1-piperazinylmethyl]-1*H*-pyrrolo[2,3-*b*]pyridine



C16 H17 Cl N6; Mol wt: 328.8053

ACTION – Potential antipsychotic agent, a dopamine receptor antagonist with selectivity for D₄ receptors relative to D₂ receptors (K_i = 0.73 nM vs. 9529 nM using [³H]-spiperone as the ligand and cells transfected with human receptors) and low affinity for a range of other receptors. Other representative compounds include the following:



Compound	R1	A	Formula
272415	I	N	C ₁₈ H ₁₇ N ₆
272416	H	N	C ₁₈ H ₁₈ N ₆
272417	Me	N	C ₁₇ H ₂₀ N ₆
272418	OMe	N	C ₁₇ H ₂₀ N ₆ O
272419	Ph	N	C ₂₂ H ₂₂ N ₆
272420	I	CH	C ₁₇ H ₁₈ N ₅

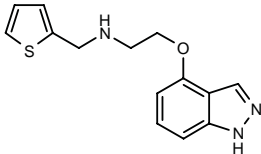
SOURCE – Resolution Pharmaceuticals.

REFERENCES

1. Pollak, A. et al. (Resolution Pharmaceuticals Inc.) *Dopamine D4 receptor ligands*. WO 9900386.

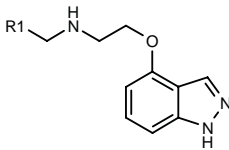
272690

N-[2-(1*H*-Indazol-4-yloxy)ethyl]-*N*-(2-thienylmethyl)amine



C14 H15 N3 O S; Mol wt: 273.3585

ACTION – A selective dopamine autoreceptor agonist, as demonstrated in a binding assay in rat striatal brain tissue using [³H]-quinpirole as the ligand (IC₅₀ = 4.30 nM), with relatively much lower affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 1092 nM against [³H]-spiroperidol binding in limbic brain tissue). Potentially useful for the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome and alcohol or drug addiction. Other specifically claimed compounds from this series of 4-aminoethoxyindazole derivatives include the following:



Compound	R1	Formula
272691	Ph	C ₁₈ H ₁₇ N ₃ O
272692	3-thienyl	C ₁₄ H ₁₅ N ₃ OS

SOURCE – American Home Products.

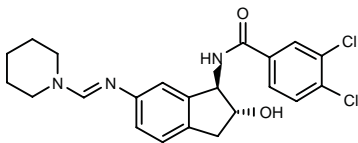
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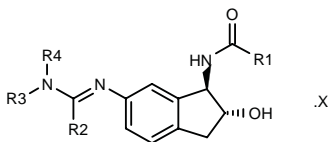
272946

trans-3,4-Dichloro-*N*-[2-hydroxy-6-[1-piperidiny]-methylenamino]-2,3-dihydro-1*H*-inden-1-yl]benzamide



C22 H23 Cl2 N3 O2; Mol wt: 432.3487

ACTION – Antipsychotic agent, a muscarinic receptor agonist with high affinity for muscarinic M₄ receptors, as demonstrated in a functional assay by measuring cAMP accumulation in pertussis toxin-treated CHO K1 cells transfected with the human m₄ receptor, where it produced 214% maximum stimulation relative to oxotremorine-M. Other compounds from this series of indane-like derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
272947	3,5-(Cl)2-Ph	H	-(CH2)4-			C ₂₁ H ₂₁ Cl ₂ N ₃ O ₂
272948	2,3,4,5-(F)4-Ph	H	-(CH2)4-			C ₂₁ H ₁₉ F ₄ N ₃ O ₂
272949	2,6-(Cl)2-Ph	H	-(CH2)4-			C ₂₁ H ₂₁ Cl ₂ N ₃ O ₂
272950	3,5-(CF3)2-Ph	H	Me	Me		C ₂₁ H ₁₉ F ₆ N ₃ O ₂
272951	1-Naph	H	Me	Me		C ₂₃ H ₂₃ N ₃ O ₂
272952	3,4-(Cl)2-Ph	Me	Me	Me		C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂
272953	4-Ph-Ph	H	-(CH2)4-			C ₂₇ H ₂₇ N ₃ O ₂
272954	4-Ph-Ph	-(CH2)3-		Me		C ₂₇ H ₂₇ N ₃ O ₂
272955	3-CF3-Ph	H	Me	Me	HCl	C ₂₀ H ₂₀ F ₃ N ₃ O ₂ ·HCl

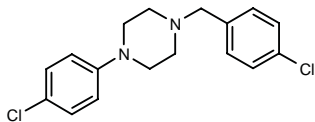
SOURCE – Lilly.

REFERENCES

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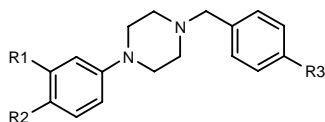
273218

1-(4-Chlorobenzyl)-4-(4-chlorophenyl)piperazine



C17 H18 Cl2 N2; Mol wt: 321.2492

ACTION – Agent for the treatment of CNS disorders including schizophrenia, psychosis, depression, Alzheimer’s disease, Parkinson’s disease, tardive dyskinesias, drug abuse, obsessive–compulsive disorder and side effects associated with the use of conventional neuroleptic agents, a highly potent and selective dopamine D₄ receptor antagonist (K_i = 5 nM) relative to D₂ receptors (K_i > 1000 nM). Within this series of 1-benzyl-4-phenylpiperazines, the following are also included:



Compound	R1	R2	R3	Formula
273219	Me	Me	Cl	C ₁₉ H ₂₃ ClN ₂
273220	H	OMe	Cl	C ₁₈ H ₂₁ ClN ₂ O
273221	H	Cl	Me	C ₁₈ H ₂₁ ClN ₂

SOURCE – Neurogen.

REFERENCES

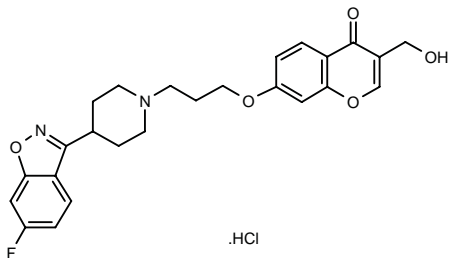
1. Thurkauf, A. and Chen, X. (Neurogen Corp.) *1-Phenyl-4-benzylpiperazines: Dopamine receptor subtype specific ligands (D4).* US 5859246, WO 9833784.

ABAPERIDONE HYDROCHLORIDE

Prop INNM

271569

7-[3-[4-(6-Fluorobenzisoxazol-3-yl)-1-piperidin-yl]propoxy]-3-(hydroxymethyl)-4*H*-1-benzopyran-4-one hydrochloride



C25 H25 F N2 O5 . HCl; Mol wt: 488.9404

ACTION – Potential atypical antipsychotic agent with high affinity for both dopamine D₂ and 5-HT_{2A} receptors (IC₅₀ = 17.0 and 6.2 nM, respectively; K_i = 12 and 1.9 nM, respectively), as well as for dopamine D₃ receptors and α₁-adrenoceptors (K_i = 5.4 and 2.4 nM, respectively), but not for α₂- or β-adrenoceptors, muscarinic and δ-receptors. *In vivo*, compound inhibited apomorphine-induced climbing in mice with an ED₅₀ of 0.24 mg/kg p.o., being as active as risperidone and about 60-fold more active than clozapine. It induced catalepsy in rats (ED₅₀ = 8.48 mg/kg p.o.) only at doses about 30 times higher than that required to inhibit apomorphine-induced climbing, indicating a reduced propensity for inducing extrapyramidal side effects. It was also associated with a lower increase in serum prolactin compared to risperidone. Selected for clinical development.

SOURCE – Ferrer.

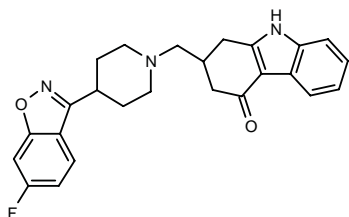
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2. Bolós, J. et al. 7-[3-(1-Piperidinyl)propoxy]chromenones as potential atypical antipsychotics. 2. Pharmacological profile of 7-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one (abaperidone, FI-8602). J Med Chem 1998, 41(27): 5402.
3. Proposed international nonproprietary names (Prop. INN): List 80. WHO Drug Inf 1998, 12(4): 252.

QF-2004B

271188

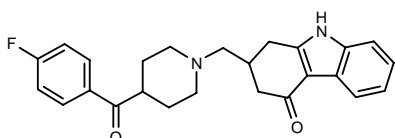
2-[4-(6-Fluorobenzisoxazol-3-yl)piperidin-1-ylmethyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one



C25 H24 F N3 O2; Mol wt: 417.4816

M.p. 222-3 °C.

ACTION – Potential atypical antipsychotic agent, a butyrophenone derivative that binds to both dopamine D₂ and 5-HT_{2A} receptors (pK_i = 6.85 and 8.80, respectively) and shows a favorable relative affinity ratio (pK_i 5-HT_{2A}/D₂ = 1.28; clozapine = 1.23). Selected for further development. Another related compound is:



QF-2003B [271187]: C25 H25 F N2 O2

SOURCE – Universidad de Santiago de Compostela, Santiago de Compostela (ES).

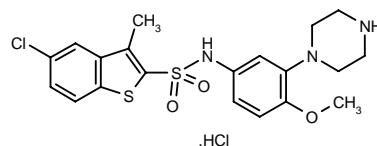
REFERENCES

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SB-271046

272387

5-Chloro-N-[4-methoxy-3-(1-piperazinyl)phenyl]-3-methyl-benzothiophene-2-sulfonamide hydrochloride



C20 H22 Cl N3 O3 S2 . HCl; Mol wt: 488.4577

ACTION – Potent and selective 5-HT₆ receptor antagonist with a pK_i of 8.9 in a binding assay using cloned human receptor and good selectivity (> 200-fold) over other 5-HT receptor subtypes, adrenoceptors, dopamine receptors, ion channels and enzymes. In a functional adenylyl cyclase assay using membranes from HeLa cells transfected with the human 5-HT₆ receptor, compound showed potent antagonist activity (pA₂ = 8.7). SB-271046 has no significant inhibitory activity against human cytochrome P-450 and it showed moderate brain penetration (10%), a good half-life (4.8 h) and high oral bioavailability (> 80%) in rats. Selected for further evaluation for potential as an antipsychotic or antidepressant agent, as well as for the treatment of memory dysfunction.

SOURCE – SmithKline Beecham.

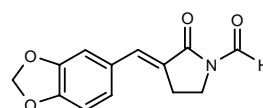
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ANTIDEPRESSANTS

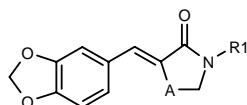
272339

3-[(E)-1,3-Benzodioxol-5-ylmethylene]-2-oxopyrrolidine-1-carbaldehyde



C13 H11 N O4; Mol wt: 245.2329

ACTION – An inhibitor of the expression of heat shock factor (HSF), a transcriptional factor that regulates the production of heat shock proteins (HSPs), potentially useful in the treatment or prevention of stress-induced diseases such as depression, as well as in the thermotherapy of cancer. A representative compound from a series of 1,3-benzodioxolyl derivatives, wherein the following are also included:



Compound	R1	A	Formula
272340	H	-CH2-	C ₁₂ H ₁₁ NO ₃
272341	H	-(CH2)2-	C ₁₃ H ₁₃ NO ₃
272342	CHO	-(CH2)2-	C ₁₄ H ₁₃ NO ₄

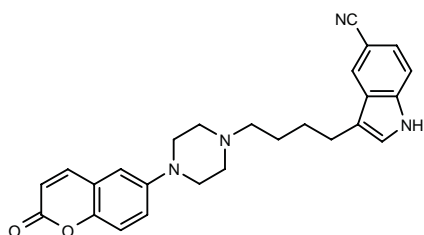
SOURCE – Kaneka.

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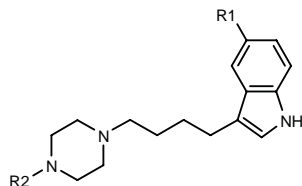
272723

3-[4-[4-(2-oxo-2H-1-benzopyran-6-yl)-1-piperazinyl]butyl]-1H-indole-5-carbonitrile



C₂₆ H₂₆ N₄ O₂; Mol wt: 426.5174

ACTION – Agent for the treatment of depression, anxiety, schizophrenia, obsessive-compulsive disorder, tardive dyskinesia, learning disorders, memory impairment, stroke and cerebral ischemia with 5-HT_{1A} receptor-agonist and 5-HT reuptake-inhibitory activity. Other specifically claimed compounds from this series of piperazine derivatives include the following:



Compound	R1	R2	Formula
272724	H	2-oxo-2H-1-benzopyran-6-yl	C ₂₅ H ₂₇ N ₃ O ₂
272726	CN	2-oxo-2H-1-benzopyran-4-yl	C ₂₆ H ₂₆ N ₄ O ₂
272727	CN	7-OH-2-oxo-2H-1-benzopyran-6-yl	C ₂₆ H ₂₆ N ₄ O ₃

SOURCE – Merck KGaA.

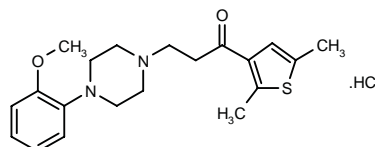
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VN-2512

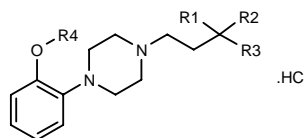
272564

1-(2,5-Dimethyl-3-thienyl)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-1-propanone hydrochloride



C₂₀ H₂₆ N₂ O₂ S . HCl; Mol wt: 394.9643

ACTION – Agent for the treatment of CNS disorders, particularly depression and anxiety, a dual 5-HT_{1A} receptor antagonist (IC₅₀ = 12 nM) and 5-HT reuptake inhibitor (IC₅₀ = 2.7 μM). Other specifically claimed compounds from this series of thiophene and benzothiophene derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
VN-2212 [272565]	-O-		3-benzothieryl	Me		C ₂₂ H ₂₄ N ₂ O ₂ S .HCl
VN-2222 [272566]	OH	H	3-benzothieryl	Me		C ₂₂ H ₂₆ N ₂ O ₂ S .HCl
VN-222H [272567]	OH	H	3-benzothieryl	H		C ₂₁ H ₂₄ N ₂ O ₂ S .HCl
VN-2382A [272568]	-N(OH)-		3-Me-2-thienyl	Me	Z	C ₁₉ H ₂₆ N ₃ O ₂ S .HCl
VN-2382B [272569]	-N(OH)-		3-Me-2-thienyl	Me	E	C ₁₉ H ₂₆ N ₃ O ₂ S .HCl
VN-7112 [272570]	-O-		3,5-(Me)2-2-benzothieryl	Me		C ₂₄ H ₂₈ N ₂ O ₂ S .HCl
VN-7122 [272571]	OH	H	3,5-(Me)2-2-benzothieryl	Me		C ₂₄ H ₃₀ N ₂ O ₂ S .HCl
VN-702H [272572]	OH	H	3-Me-2-benzothieryl	H		C ₂₂ H ₂₆ N ₂ O ₂ S .HCl

SOURCE – Vita Elan.

REFERENCES

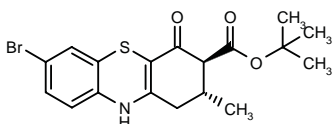
1. Monge Vega, A. et al. (Vita Elan Farma) *Cpds. derived from thiophene and benzothiophene, and related utilisation and compsn*. WO 9902516.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

271522

trans-7-Bromo-2-methyl-4-oxo-2,3,4,10-tetrahydro-1*H*-phenothiazine-3-carboxylic acid *tert*-butyl ester



C18 H20 Br N O3 S; Mol wt: 410.3300

ACTION – Anticonvulsant with strong and long-lasting (4 h) protective activity against maximal electroshock seizures (MES) in mice, preventing convulsions in 3 of 3 and 2 of 3 animals, respectively, at 30 min and 4 h following a dose of 100 mg/kg i.p.; it showed no neurological toxicity at up to 300 mg/kg i.p. In rats, compound given orally also protected from MES with an ED_{50} of 17.6 mg/kg and no neurological toxicity at up to 500 mg/kg; its protective index ($PI = TD_{50}/ED_{50} > 28.4$) was higher than that of phenytoin ($PI = 6.9$) and carbamazepine ($PI = 8.1$). Compound was not active against picrotoxin- or bicuculline-induced convulsions, indicating a mechanism of action independent of GABA and chloride channel interactions.

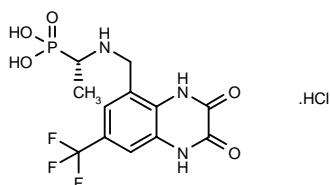
SOURCES – DuPont Pharmaceuticals; 3M Pharmaceuticals.

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272005

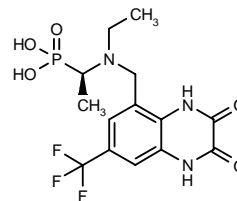
1(*S*)-[2,3-dioxo-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxalin-5-ylmethylamino]ethylphosphonic acid hydrochloride



C12 H13 F3 N3 O5 P . HCl; Mol wt: 403.6796

ACTION – Anticonvulsant with high affinity for the glycine binding site of the NMDA receptor complex ($IC_{50} = 6$ nM against [3H]-MDL-105519 binding) and moderate affinity for AMPA receptors ($IC_{50} = 1.2$ μ M against [3H]-AMPA binding). In the mouse electroshock-induced convulsion model, compound exhibited potent anticonvulsant activity

($ED_{50} = 8$ mg/kg i.p.). Another related compound from this series of *N*-phosphonoalkyl-5-aminomethylquinoxaline-2,3-diones is:



272006: C14 H17 F3 N3 O5 P

SOURCE – Novartis.

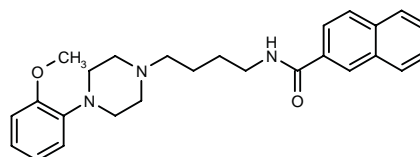
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

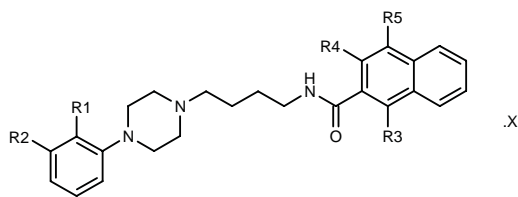
272697

N-[4-[4-(2-Methoxyphenyl)-1-piperazinyl]butyl]-2-naphthalenecarboxamide



C26 H31 N3 O2; Mol wt: 417.5499

ACTION – Agent for the treatment of psychosis, depression, drug dependence, male impotence and, particularly, Parkinson's disease, a potent partial agonist at dopamine D_3 receptors with an EC_{50} value of 3 nM and an intrinsic activity of 60% that of dopamine in a test measuring [3H]-thymidine incorporation into CHO cells expressing the human D_3 receptor, reported to possess 25-fold lower affinity for dopamine D_2 receptors. Other specifically claimed compounds from this series of 2-naphthamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
272698	OMe	H	OMe	H	NO2		C ₂₇ H ₃₂ N ₄ O ₅
272699	OMe	H	OMe	H	CN		C ₂₈ H ₃₂ N ₄ O ₃
272700	Cl	H	H	OMe	H		C ₂₆ H ₃₀ ClN ₃ O ₂
272701	Cl	H	H	H	H		C ₂₅ H ₂₆ ClN ₃ O
272703	H	Cl	H	H	H		C ₂₅ H ₂₆ ClN ₃ O
272704	H	H	H	H	H		C ₂₅ H ₂₉ N ₃ O
272705	OMe	H	OMe	H	H	oxalate	C ₂₇ H ₃₃ N ₃ O ₃ .C ₂ H ₂ O ₄

SOURCES – Bioprojet; INSERM.

REFERENCES

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ENTACAPONE+

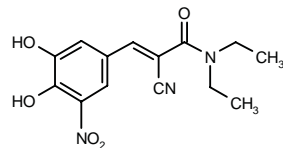
178077

(E)-2-Cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)propenamide

(E)-2-Cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide

(E)-α-Cyano-N,N-diethyl-3,4-dihydroxy-5-nitrocinnamamide

OR-611



C14 H15 N3 O5; Mol wt: 305.2885

ACTION – Antiparkinsonian agent, a peripheral catechol-O-methyltransferase (COMT) inhibitor that prevents the breakdown of levodopa.

INDICATION – Treatment of Parkinson’s disease in combination with levodopa/dopa decarboxylase inhibitor.

PRESENTATION – Tablets, 200 mg.

PROPRIETARY NAME – Comtess (DE, FI, GB, SE).

SOURCES – Orion; licensed to Novartis (Comtan) for most markets except the Nordic countries, Germany, the U.K., Ireland and the Baltic countries.

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21. Orion launches entacapone in first markets and updates safety information. DailyDrugNews.com (Daily Essentials) 1998, Dec 1.

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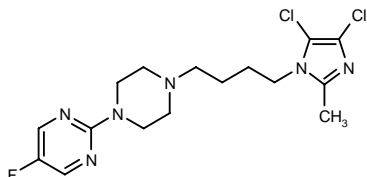
MONOGRAPH – Prous, J. et al. Entacapone. Drugs Fut 1994, 19(7): 641.

†Drug Data Report 1992, 014(02): 0109.

TREATMENT OF NAUSEA AND VOMITING

272897

2-[4-[4-(4,5-Dichloro-2-methyl-1*H*-imidazol-1-yl)butyl]-1-piperazinyl]-5-fluoropyrimidine



C₁₆ H₂₁ Cl₂ F N₆; Mol wt: 387.2879

ACTION – 5-HT_{1A} receptor agonist (K_i = 19.4 nM) with antiemetic, anxiolytic, antidepressive and antisecretory properties. Antiemetic activity was demonstrated by inhibition of CuSO₄ and cisplatin-induced vomiting in ferrets at 0.001-1 mg/kg s.c. Compound was also effective in a model of motion sickness in *Suncus murinus* at 0.001-10 mg/kg i.p. Anxiolytic activity was demonstrated in the conditioned avoidance test in rats, giving an ED₅₀ value of 9.7 mg/kg p.o. In addition, compound was also found to significantly inhibit gastric acid secretion in pylorus-ligated rats (ED₅₀ = 1.9 mg/kg i.d.).

SOURCE – Esteve.

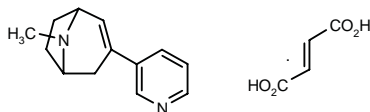
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COGNITION-ENHANCING DRUGS

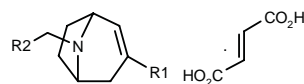
271863

(±)-8-Methyl-3-(3-pyridyl)-8-azabicyclo[3.2.1]oct-2-ene fumarate



C₁₃ H₁₆ N₂ . C₄ H₄ O₄; Mol wt: 316.3550

ACTION – Nicotinic acetylcholine receptor (nAChR) ligand whose affinity was tested in three *in vitro* binding assays using rat brain preparations as the source of receptors and [³H]-cytisine ($\alpha 4$ and $\beta 2$ subunit-containing receptors), [³H]-epibatidine ($\alpha 4\beta 2$ subtype) and [³H]- α -bungarotoxin ($\alpha 7$ and $\alpha 1$ subunit-containing receptors) as the ligands (IC_{50} = 0.023, 0.084 and 0.500 μ M, respectively). Potentially useful for the treatment of CNS disorders such as Alzheimer's disease, Parkinson's disease, memory dysfunction and attention deficit hyperactivity disorder, as well as chemical substance abuse or withdrawal symptoms. Within this series of specifically claimed 8-azabicyclo[3.2.1]oct-2-ene and octane derivatives, the following are also included:



Compound	R1	R2	Formula
271864	3-Pyr	Ph	C ₂₃ H ₂₄ N ₂ O ₄
271865	6-Cl-3-Pyr	H	C ₁₇ H ₁₉ ClN ₂ O ₄
271866	3-NH2-Ph	H	C ₁₈ H ₂₂ N ₂ O ₄

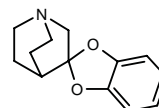
SOURCE – NeuroSearch.

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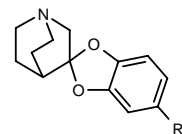
271867

Spiro[1,3-benzodioxole-2,3'-quinuclidine]



C₁₃ H₁₅ N O₂; Mol wt: 217.2665

ACTION – Agent with affinity for nicotinic acetylcholine (nACh) receptors, particularly those containing the $\alpha 7$ subunit (brain) and the $\alpha 1$ subunit (neuromuscular junction), as demonstrated in three *in vitro* binding assays using rat brain preparations as the source of receptors and [³H]-cytisine, [³H]- α -bungarotoxin and [³H]-epibatidine as the ligands (IC_{50} = 30.0, 0.19 and 175 μ M, respectively). Potentially useful for the treatment of Alzheimer's disease, Parkinson's disease, memory dysfunction, attention deficit hyperactivity disorder and chemical substance abuse or withdrawal symptoms. Other specifically claimed spiroquinuclidine derivatives include the following:



Compound	R1	Formula
271868	Me	C ₁₄ H ₁₇ NO ₂
271869	t-Bu	C ₁₇ H ₂₃ NO ₂

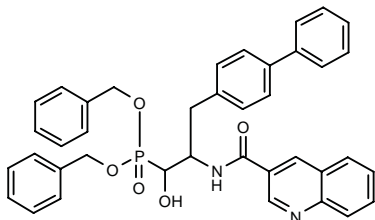
SOURCE – NeuroSearch.

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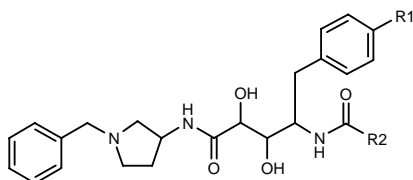
272575

3-(Biphenyl-4-yl)-1-hydroxy-2-(3-quinolinylcarbox-amido)propylphosphonic acid bis(benzyl) ester

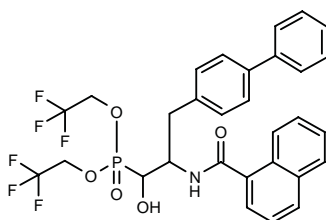


C39 H35 N2 O5 P; Mol wt: 642.6885

ACTION – Selective inhibitor of the aspartyl proteases plasmepsin and cathepsin D, claimed for the treatment of Alzheimer's disease and malaria. Other compounds from this series of glycol and hydroxyphosphonate peptidomimetics include the following:



Compound	R1	R2	Formula
272577	Ph	CH(i-Pr)OCONHCH2CH2Ph	C ₄₂ H ₅₀ N ₄ O ₆
272578	Cl	2,4-(MeO)2-Ph	C ₃₁ H ₃₆ ClN ₃ O ₆



272576: C30 H26 F6 N O5 P

Plasmepsin I and II are proteases from *Plasmodium falciparum* required during the initial stages of hemoglobin hydrolysis and digestion, and cathepsin D is believed to be the protease that processes β -amyloid precursor protein.

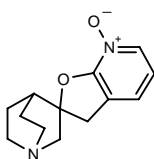
SOURCE – Pharmacopeia.

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272708

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo-[2,3-b]pyridine] 7'-oxide



C13 H16 N2 O2; Mol wt: 232.2814

ACTION – A selective $\alpha 7$ nicotinic acetylcholine receptor (nAChR) agonist with potential in the treatment or prevention of cognitive disorders such as Alzheimer's disease, attention deficit hyperactivity disorder and memory loss, and psychotic disorders such as schizophrenia, mania and anxiety. Compound may also be useful as an analgesic, as well as in the treatment or prevention of Parkinson's disease, Huntington's disease, Tourette's syndrome, jet lag and in smoking cessation. A representative compound from a series of spiroazabicyclic heterocyclic derivatives.

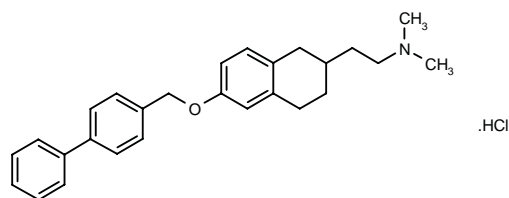
SOURCE – Astra (AstraZeneca).

REFERENCES

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272732

N-[2-[6-(Biphenyl-4-ylmethoxy)-1,2,3,4-tetrahydro-2-naphthyl]ethyl]-N,N-dimethylamine hydrochloride



C27 H31 N O . HCl; Mol wt: 422.0088

ACTION – Agent for the treatment of neurodegenerative disorders such as Alzheimer's disease, an inhibitor of the production and/or secretion of β -amyloid protein (about 75% inhibition of A β 1-40 and A β 1-42 production in human neuroblastoma IMR-32 cells at 10 μ M).

SOURCE – Takeda.

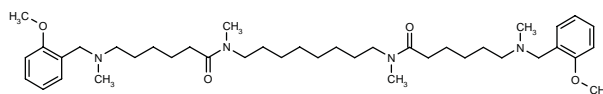
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CAPROCTAMINE

269885

N,N'-Octamethylenebis[6-[N-(2-methoxybenzyl)-N-methylamino]-N-methylhexanamide]



C40 H66 N4 O4; Mol wt: 666.9854

Citrate salt, oil.

ACTION – Dual acetylcholinesterase (AChE) inhibitor ($pIC_{50} = 6.77$; $K_i = 0.104 \mu M$) and competitive muscarinic receptor antagonist with higher activity at M_2 than at M_1 and M_3 receptors ($pA_2 = 6.39, 5.66$ and 5.55 , respectively); its inhibitory effect against AChE was similar to that of the known compound tacrine ($K_i = 0.151 \mu M$) and it showed mixed-type enzyme inhibition, inhibiting both the active and the distal site of the enzyme. Compound was significantly less active against butyrylcholinesterase (BChE; $pIC_{50} = 4.93$). It is suggested to have potential in the treatment of Alzheimer's disease, and may be able to stimulate cholinergic activity in the brain by decreasing ACh hydrolysis and simultaneously increasing ACh release in the synapse; it may also be able to prevent AChE-mediated β -amyloid peptide aggregation via an interaction with the peripheral binding site of AChE.

SOURCE – Università degli Studi di Bologna, Bologna (IT).

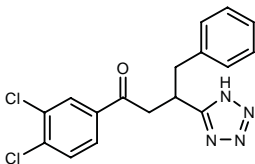
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PNU-168778

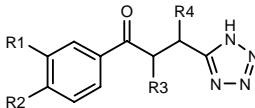
272501

1-(3,4-Dichlorophenyl)-4-phenyl-3-(1*H*-tetrazol-5-yl)-1-butanone



C17 H14 Cl2 N4 O; Mol wt: 361.2306

ACTION – Agent for the treatment of neurodegenerative disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy and dementia that acts as a kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor, as demonstrated *in vitro* in rat liver mitochondrial extracts ($IC_{50} = 2.32 \mu M$). Other specifically claimed compounds within this series of 5-(3-phenyl-3-oxopropyl)-1*H*-tetrazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
272503	F	H	H	H	C ₁₀ H ₉ FN ₄ O
272504	Cl	H	H	H	C ₁₀ H ₉ ClN ₄ O
272505	Br	H	H	H	C ₁₀ H ₉ BrN ₄ O
272507	Cl	Cl	H	H	C ₁₀ H ₈ Cl ₂ N ₄ O
272508	F	F	H	H	C ₁₀ H ₈ F ₂ N ₄ O
272509	Cl	Cl	-CH2-		C ₁₁ H ₈ Cl ₂ N ₄ O
272510	F	F	-CH2-		C ₁₁ H ₈ F ₂ N ₄ O

SOURCE – Pharmacia & Upjohn.

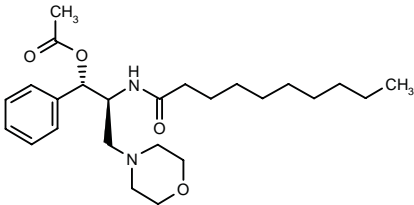
REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *5-(3-Phenyl-3-oxo-propyl)-1H-tetrazole derivs*. WO 9902506.

TREATMENT OF CEREBROVASCULAR DISEASES

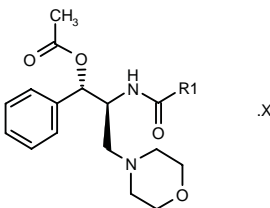
271427

Acetic acid (1*S*,2*S*)-2-(decanamido)-3-(4-morpholinyl)-1-phenylpropyl ester



C25 H40 N2 O4; Mol wt: 432.6010

ACTION – Neuroprotective agent able to protect rats from disturbances of spatial perception memory caused by brain ischemia at a dose of 2 mg/kg i.v. Compound also displayed neurite growth-potentiating activity, as demonstrated *in vitro* in cerebral cortex cell suspensions prepared from rat fetuses. Within this series of aminoalcohol derivatives, the following are also included:



Compound	R1	X	Formula
271429	C9H19	HCl	C ₂₅ H ₄₀ N ₂ O ₄ .HCl
271431	OC8H17		C ₂₄ H ₃₈ N ₂ O ₅

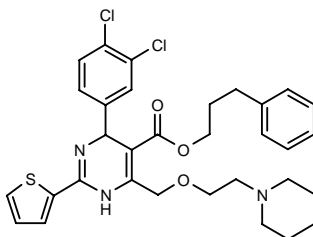
SOURCE – Seikagaku.

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1. Inoguchi, J. et al. (Seikagaku Corp.) *Aminoalcohol derivs. and medicines containing them*. JP 98324671.

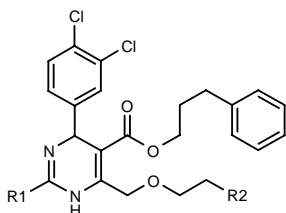
272261

4-(3,4-Dichlorophenyl)-6-[2-(1-piperidinyl)ethoxymethyl]-2-(2-thienyl)-1,4-dihydropyrimidine-5-carboxylic acid 3-phenylpropyl ester



C32 H35 Cl2 N3 O3 S; Mol wt: 612.6185

ACTION – N-type neuronal calcium channel blocker with potential in the treatment or prevention of cerebrovascular ischemia, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and AIDS-related dementia, pain, attention disorders, psychotic disorders such as schizophrenia, affective disorders such as anxiety and depression, and migraine. Other exemplified compounds from this series of dihydropyrimidine derivatives include the following:



Compound	R1	R2	Formula
272262	2-furyl	1-Pip	C ₃₂ H ₃₅ Cl ₂ N ₃ O ₄
272263	4-Pyr	1-Pip	C ₃₃ H ₃₆ Cl ₂ N ₄ O ₃
272264	2-furyl	N(Et)2	C ₃₁ H ₃₅ Cl ₂ N ₃ O ₄
272265	2-furyl	4-Me-1-Piz	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₄
272266	4-Cl-Ph	1-Pip	C ₃₄ H ₃₆ Cl ₃ N ₃ O ₃
272267	4-Me-Ph	1-Pip	C ₃₅ H ₃₉ Cl ₂ N ₃ O ₃

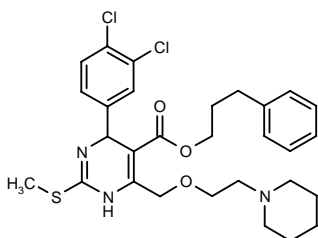
SOURCE – Astra (AstraZeneca).

REFERENCES

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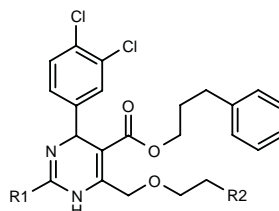
272268

4-(3,4-Dichlorophenyl)-2-(methylsulfanyl)-6-[2-(1-piperidinyl)ethoxymethyl]-1,4-dihydropyrimidine-5-carboxylic acid 3-phenylpropyl ester



C29 H35 Cl2 N3 O3 S; Mol wt: 576.5855

ACTION – N-type neuronal calcium channel blocker with potential in the treatment or prevention of cerebrovascular ischemia, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and AIDS-related dementia, pain, attention disorders, psychotic disorders such as schizophrenia, affective disorders such as anxiety and depression, and migraine. Other exemplified compounds from this series of dihydropyrimidine derivatives include the following:



Compound	R1	R2	Formula
272269	OMe	1-Pip	C ₂₉ H ₃₅ Cl ₂ N ₃ O ₄
272270	4-MeO-PhCH2S	1-Pip	C ₃₈ H ₄₁ Cl ₂ N ₃ O ₄ S
272271	N(Me)2	1-Pip	C ₃₀ H ₃₈ Cl ₂ N ₄ O ₃
272272	SMe	NH2	C ₂₄ H ₂₇ Cl ₂ N ₃ O ₃ S
272273	SMe	1-Me-1-Pip Cl'	C ₃₀ H ₃₈ Cl ₃ N ₃ O ₃ S

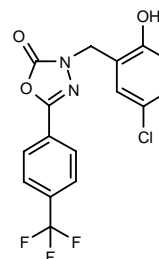
SOURCE – Astra (AstraZeneca).

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1. Michne, W.F. and Pierson, M.E. Jr. (Astra AB) *Compounds.* WO 9901437.

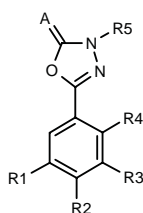
272624

3-(5-Chloro-2-hydroxybenzyl)-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3H)-one



C16 H10 Cl F3 N2 O3; Mol wt: 370.7130

ACTION – Agent for the treatment of cerebral ischemia, convulsions, asthma, irritable bowel syndrome, migraine, traumatic brain injury, male erectile dysfunction and urinary incontinence that acts as an opener of large-conductance Ca²⁺-activated potassium channels (Maxi-K or BK_{Ca} channels). It produced a 125-175% increase in BK_{Ca} current in *Xenopus* oocytes. *In vivo* neuroprotective activity was evaluated in the focal stroke model involving permanent middle cerebral artery occlusion (MCAO) in spontaneously hypertensive rats, where compound produced an approximately 14% reduction in cortical infarct volume at 10 mg/kg i.p. 2 h after MCAO. Other specifically claimed compounds from this series of diphenyl oxadiazolones include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
272625	H	CF ₃	H	H	2-OH-5-Cl-PhCH ₂	S	C ₁₆ H ₁₀ ClF ₃ N ₂ O ₂ S
272626	Cl	Cl	H	H	2-OH-4-NH ₂ -5-Cl-PhCH ₂	O	C ₁₅ H ₁₀ Cl ₃ N ₃ O ₃
272627	Cl	H	Cl	H	2-OH-4-NH ₂ -5-Cl-PhCH ₂	O	C ₁₅ H ₁₀ Cl ₃ N ₃ O ₃
272628	Cl	NH ₂	H	OH	4-CF ₃ -Ph	O	C ₁₅ H ₉ ClF ₃ N ₃ O ₃

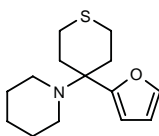
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Romine, J.L. et al. (Bristol-Myers Squibb Co.) *Diphenyl oxadiazolones as potassium channel modulators*. US 5869509.

272894

1-[4-(2-Furyl)tetrahydrothiopyran-4-yl]piperidine



C₁₄ H₂₁ N O S; Mol wt: 251.3919

ACTION – Neuroprotective agent and anticonvulsant with potent and selective affinity for the low-affinity phencyclidine (PCP) receptor (PCP site 3; IC₅₀ = 13.8 nM in rat cerebellum) relative to PCP sites 1 and 2 (IC₅₀ = 133 and 1015 nM in rat cortex and rat cerebellum, respectively). A representative compound from a series of phencyclidine derivatives.

SOURCE – SCRAS.

REFERENCES

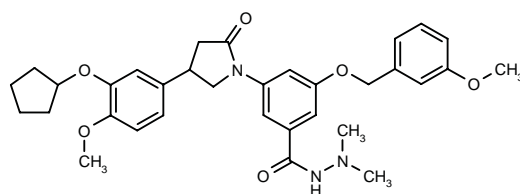
1. Kamenka, J.-M. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel phencyclidine derivs., preparation methods and pharmaceutical compsns. containing same*. WO 9855478.

RESPIRATORY DRUGS

ASTHMA THERAPY

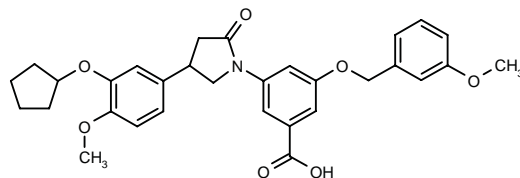
270654

3-[4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-oxopyrrolidin-1-yl]-5-(3-methoxybenzyloxy)-N²,N²-dimethylbenzohydrazide



C₃₃ H₃₉ N₃ O₆; Mol wt: 573.6861

ACTION – Antiasthmatic agent, a potent phosphodiesterase type 4 (PDE4) inhibitor derived from rolipram with nanomolar activity against all PDE4 isozymes (pIC₅₀ = 8.6, 8.3 and 8.8 against PDE4A, PDE4B and PDE4D, respectively) and at least 10,000-fold selectivity over PDE3. In human peripheral blood mononuclear cells, it strongly inhibited anti-CD3 antibody-induced T-cell proliferation, IL-4 and interferon gamma release (pI₅₀ = 7.3, 7.6 and 7.8, respectively), as well as tumor necrosis factor (TNF-α) production induced by lipopolysaccharide (LPS; pIC₅₀ = 7.7). In human eosinophils, compound inhibited the fMLP-induced oxidative burst with a pIC₅₀ of 7.3. Compared to rolipram, it showed improved potency against PDE and a better pharmacological profile. In ovalbumin-sensitized rats, compound administered intratracheally (3.2 mg/kg) 1 h before and 24 h after challenge with ovalbumin significantly inhibited both eosinophilia and eosinophil peroxidase content in bronchoalveolar lavage. Another compound from this series of rolipram derivatives is:

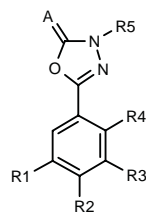


270655: C₃₁ H₃₃ N O₇

SOURCE – Novartis.

REFERENCES

1. Bacher, E. et al. *N-Arylrolipram derivatives as potent and selective PDE4 inhibitors*. Bioorg Med Chem Lett 1998, 8(22): 3229.



Compound	R1	R2	R3	R4	R5	A	Formula
272625	H	CF3	H	H	2-OH-5-Cl-PhCH2	S	C ₁₆ H ₁₀ ClF ₃ N ₂ O ₂ S
272626	Cl	Cl	H	H	2-OH-4-NH2-5-Cl-PhCH2	O	C ₁₅ H ₁₀ Cl ₃ N ₃ O ₃
272627	Cl	H	Cl	H	2-OH-4-NH2-5-Cl-PhCH2	O	C ₁₅ H ₁₀ Cl ₃ N ₃ O ₃
272628	Cl	NH2	H	OH	4-CF3-Ph	O	C ₁₅ H ₉ ClF ₃ N ₃ O ₃

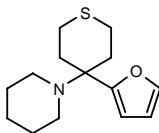
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Romine, J.L. et al. (Bristol-Myers Squibb Co.) *Diphenyl oxadiazolones as potassium channel modulators*. US 5869509.

272894

1-[4-(2-Furyl)tetrahydrothiopyran-4-yl]piperidine



C14 H21 N O S; Mol wt: 251.3919

ACTION – Neuroprotective agent and anticonvulsant with potent and selective affinity for the low-affinity phencyclidine (PCP) receptor (PCP site 3; IC₅₀ = 13.8 nM in rat cerebellum) relative to PCP sites 1 and 2 (IC₅₀ = 133 and 1015 nM in rat cortex and rat cerebellum, respectively). A representative compound from a series of phencyclidine derivatives.

SOURCE – SCRAS.

REFERENCES

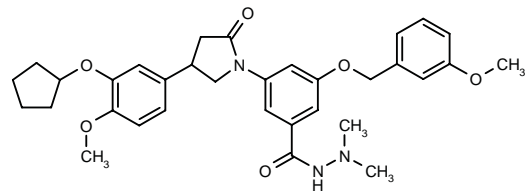
1. Kamenka, J.-M. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel phencyclidine derivs., preparation methods and pharmaceutical compsns. containing same*. WO 9855478.

RESPIRATORY DRUGS

ASTHMA THERAPY

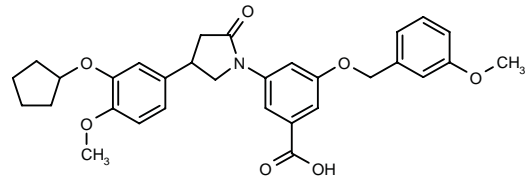
270654

3-[4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-oxopyrrolidin-1-yl]-5-(3-methoxybenzyloxy)-N²,N²-dimethylbenzohydrazide



C33 H39 N3 O6; Mol wt: 573.6861

ACTION – Antiasthmatic agent, a potent phosphodiesterase type 4 (PDE4) inhibitor derived from rolipram with nanomolar activity against all PDE4 isozymes (pIC₅₀ = 8.6, 8.3 and 8.8 against PDE4A, PDE4B and PDE4D, respectively) and at least 10,000-fold selectivity over PDE3. In human peripheral blood mononuclear cells, it strongly inhibited anti-CD3 antibody-induced T-cell proliferation, IL-4 and interferon gamma release (pI₅₀ = 7.3, 7.6 and 7.8, respectively), as well as tumor necrosis factor (TNF-α) production induced by lipopolysaccharide (LPS; pIC₅₀ = 7.7). In human eosinophils, compound inhibited the fMLP-induced oxidative burst with a pIC₅₀ of 7.3. Compared to rolipram, it showed improved potency against PDE and a better pharmacological profile. In ovalbumin-sensitized rats, compound administered intratracheally (3.2 mg/kg) 1 h before and 24 h after challenge with ovalbumin significantly inhibited both eosinophilia and eosinophil peroxidase content in bronchoalveolar lavage. Another compound from this series of rolipram derivatives is:



270655: C31 H33 N O7

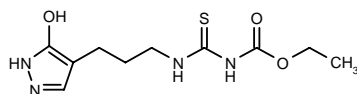
SOURCE – Novartis.

REFERENCES

1. Bacher, E. et al. *N-Arylrolipram derivatives as potent and selective PDE4 inhibitors*. Bioorg Med Chem Lett 1998, 8(22): 3229.

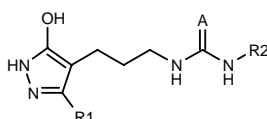
271694

N'-[3-(5-Hydroxy-1*H*-pyrazol-4-yl)propyl]thiourea-*N*-carboxylic acid ethyl ester



C10 H16 N4 O3 S; Mol wt: 272.3274

ACTION – Antiallergic and antiasthmatic agent proven to selectively inhibit the release of eosinophil peroxidase from fMLP-stimulated guinea pig eosinophils *in vitro* (46.3 and 95.6% inhibition at 0.1 and 1 μ M, respectively), as compared to the release of histamine from ovalbumin-induced rat peritoneal mastocytes (37.1% inhibition at 1 μ M). *In vivo*, it produced 22.0 and 53.0% inhibition, respectively, of the immediate asthmatic response to antigen in sensitized guinea pigs at 0.1 and 1.0 mg/kg i.v. Within this series of pyrazole derivatives, the following are also included:



Compound	R1	R2	A	Formula
271696	H	COPh	O	C ₁₄ H ₁₆ N ₄ O ₃
271697	Me	3-CF ₃ -Ph	S	C ₁₅ H ₁₇ F ₃ N ₄ OS
271698	H	3-Me-Ph	S	C ₁₄ H ₁₈ N ₄ OS
271699	H	Ph	O	C ₁₃ H ₁₆ N ₄ O ₂
271700	H	2-CF ₃ O-Ph	O	C ₁₄ H ₁₅ F ₃ N ₄ O ₃
271701	H	4-CF ₃ O-Ph	O	C ₁₄ H ₁₅ F ₃ N ₄ O ₃

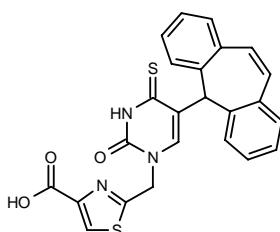
SOURCE – Kaken.

REFERENCES

1. Ishige, H. et al. (Kaken Pharmaceutical Co., Ltd.) *Pyrazole derivs.* JP 98287655.

271886

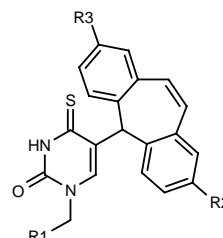
2-[5-(5*H*-Dibenzo[*a,d*]cyclohepten-5-yl)-2-oxo-4-thioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]thiazole-4-carboxylic acid



C24 H17 N3 O3 S2; Mol wt: 459.5483

ACTION – Purinoceptor P2 receptor antagonist with particular affinity for the P2Y₂ receptor, potentially useful for the treatment or prevention of a broad range of inflammatory diseases such as asthma, inflammatory bowel disease, psoriasis, rheumatoid arthritis, myocardial ischemia, atherosclerosis, restenosis, periodontal disease

and septic shock, as well as for the treatment of cancer. Other specifically claimed compounds from this series of substituted 1,2,3,4-tetrahydropyrimidine derivatives include the following:



Compound	R1	R2=R3	Formula
271887	4-(5-tetrazolyl)-2-thiazolyl	H	C ₂₄ H ₁₇ N ₇ OS ₂
271888	4-CO ₂ H-2-thiazolyl	Me	C ₂₆ H ₂₁ N ₃ O ₃ S ₂
271889	4-(-CO-Asp-OH)-2-thiazolyl	Me	C ₃₀ H ₂₆ N ₄ O ₆ S ₂
271890	5-[4-[4-(CH ₂ CO ₂ H)-2-thiazolyl-NH-COCH ₂]-2-thiazolyl-NHCO]-2-furyl	Me	C ₃₇ H ₃₀ N ₆ O ₆ S ₃
271891	4-CO ₂ H-2-thiazolyl	Et	C ₂₈ H ₂₅ N ₃ O ₃ S ₂

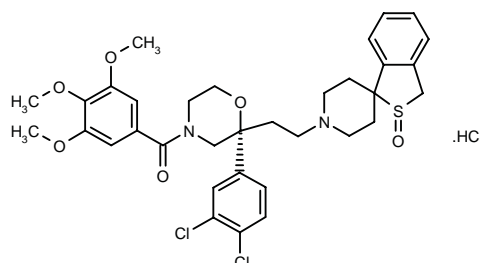
SOURCE – Astra (AstraZeneca).

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1. Kindon, N. et al. (Astra Pharmaceuticals Ltd.; Astra AB) *Novel cpds.* WO 9854180.

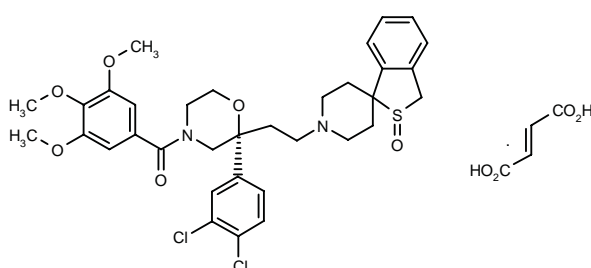
272066

1'-[2-[2(*R*)-(3,4-Dichlorophenyl)-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl]ethyl]spiro[benzo[*c*]thiophen-1(3*H*)-4'-piperidine] *S*-oxide hydrochloride



C34 H38 Cl2 N2 O6 S . HCl; Mol wt: 710.1151

ACTION – Novel salt of a known neurokinin NK₁ and NK₂ receptor antagonist* with good oral absorption and remarkable antagonist activity. *In vivo*, it gave ID₅₀ values of 5.1 mg/kg p.o. for inhibition of the substance P-induced increase in vascular permeability in guinea pigs, and of 0.51 mg/kg p.o. when tested for its ability to inhibit NKA-induced bronchoconstriction in guinea pigs. Another salt of the known optically active sulfoxide derivative is:



272067: C34 H38 Cl2 N2 O6 S . C4 H4 O4

SOURCE – Sankyo.

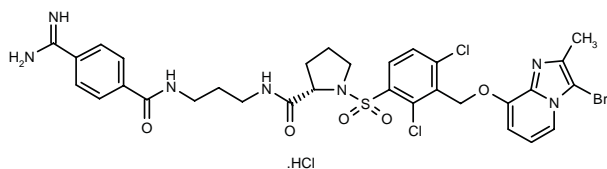
REFERENCES

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*267887 (see 267886) Drug Data Report 1998, 020(10): 0850.

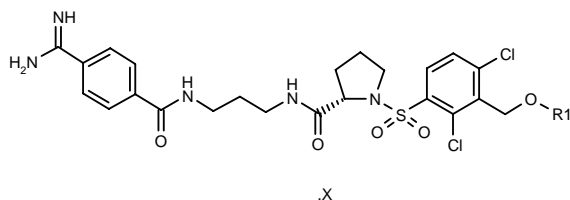
272407

N-[3-(4-Amidinobenzamido)propyl]-1-[3-(3-bromo-2-methylimidazo[1,2-*a*]pyridin-8-yloxymethyl)-2,4-dichlorophenylsulfonyl]-L-prolinamide hydrochloride

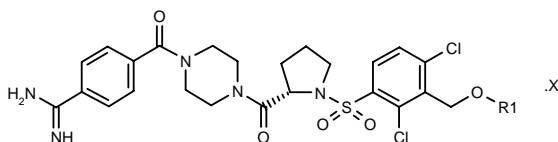


C31 H32 Br Cl2 N7 O5 S . HCl; Mol wt: 801.9747

ACTION – Bradykinin B₂ receptor antagonist for the treatment of pain, inflammation, and more particularly, asthma, traumatic brain injury and allergic rhinitis. Activity was assessed in conventional *in vitro* tests (functional and receptor binding tests), giving a pK_B value of 9.1 when assessed for its ability to inhibit guinea pig ileum contractions elicited by bradykinin. Within this series of *N*-benzenesulfonyl-L-proline derivatives, the following are also included:



Compound	R1	X	Formula
272408	2,3-(Me)2-imidazo-[1,2- <i>a</i>]pyridin-8-yl	MeSO3H	C ₃₂ H ₃₅ Cl ₂ N ₇ O ₅ S .CH ₄ O ₃ S
272410	3-Me-5-quinoxaliny		C ₃₂ H ₃₃ Cl ₂ N ₇ O ₅ S
272411	2-Me-4-oxo-4H-pyrido[1,2- <i>a</i>]pyrimidin-9-yl	2MeSO3H	C ₃₂ H ₃₃ Cl ₂ N ₇ O ₆ S .2CH ₄ O ₃ S



Compound	R1	X	Formula
272409	3-Br-2-Me-imidazo-[1,2- <i>a</i>]pyridin-8-yl	HCl	C ₃₂ H ₃₂ BrCl ₂ N ₇ O ₅ S .HCl
272412	2-Me-4-oxo-4H-pyrido[1,2- <i>a</i>]pyrimidin-9-yl	2MeSO3H	C ₃₃ H ₃₃ Cl ₂ N ₇ O ₆ S .2CH ₄ O ₃ S

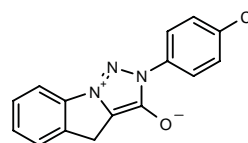
SOURCE – Fournier.

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1. Dodey, P. et al. (Fournier Industrie et Santé) *Novel N-benzenesulphonyl-L-proline cpds., preparation method and use in therapy.* WO 9900387.

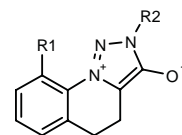
272585

2-(4-Chlorophenyl)-2*H*,4*H*-[1,2,3]triazolo[1,5-*a*]indol-9-ium-3-olate inner salt

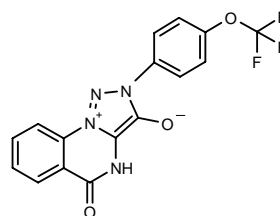


C15 H10 Cl N3 O; Mol wt: 283.7170

ACTION – Antiallergic, antiinflammatory and anti-asthmatic agent reported to be active in a chronic graft-versus-host disease test in mice and in inhibiting eosinophil infiltration into the lungs induced by ovalbumin in sensitized rats and mice. A representative compound from a series of triazole derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	Formula
272588	H	4-Cl-2-Me-Ph	C ₁₇ H ₁₄ ClN ₃ O
272589	H	4-CF ₃ -Ph	C ₁₇ H ₁₂ F ₃ N ₃ O
272590	F	4-CF ₃ -Ph	C ₁₇ H ₁₁ F ₄ N ₃ O
272591	F	6-Cl-3-Pyr	C ₁₅ H ₁₀ ClFN ₄ O



272592: C16 H9 F3 N4 O3

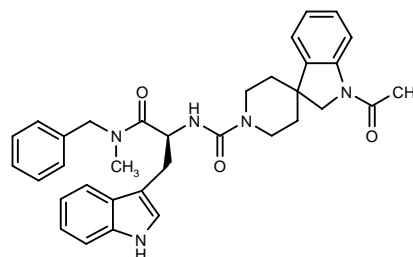
SOURCE – Astra (AstraZeneca).

REFERENCES

1. Cooke, A. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds.* WO 9902528.

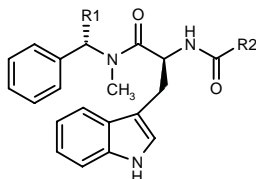
272631

N^α-(1-Acetylspiro[indoline-3,4'-piperidin]-1'-ylcarbonyl)-L-tryptophan *N*-benzyl-*N*-methylamide



C34 H37 N5 O3; Mol wt: 563.6983

ACTION – Agent for the treatment of asthma, inflammatory disorders, pain or migraine that acts by virtue of its antagonist activity at tachykinin receptors, particularly NK₁ and NK₂ receptors (IC₅₀ = 15 and 30 nM, respectively). Within this series of specifically claimed tryptophan derivatives, the following are also included:



Compound	R1	R2	Formula
272632	H	4-(2-MeO-Ph)-1-Piz	C ₃₁ H ₃₅ N ₅ O ₃
272633	H	4-(2-Me-Ph)-1-Piz	C ₃₁ H ₃₅ N ₅ O ₂
272634	Me	1-(MeSO ₂)-spiro[indoline-3,4'-piperidin]-1-yl	C ₃₄ H ₃₉ N ₅ O ₄ S

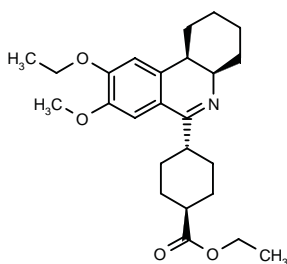
SOURCE – Merck & Co.

REFERENCES

1. Shah, S.K. et al. (Merck & Co., Inc.) *Tryptophan ureas as neurokinin antagonists*. US 5869489.

272872

(±)-*trans*-4-[*cis*-9-Ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl]cyclohexanecarboxylic ethyl ester



C₂₅ H₃₅ N O₄; Mol wt: 413.5545

ACTION – Agent for the treatment of airways disorders such as asthma and bronchitis, a selective inhibitor of phosphodiesterase type 4 (PDE4; -logIC₅₀ = 7.47). A representative compound from a series of substituted 6-alkylphenanthridines.

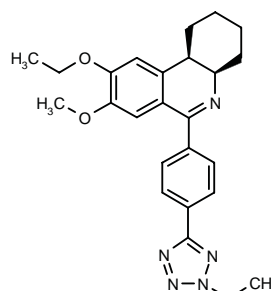
SOURCE – Byk Gulden.

REFERENCES

1. Amschler, H. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Substd. 6-alkylphenanthridines*. WO 9905112.

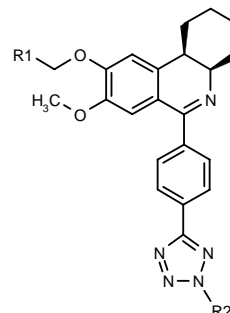
272873

(±)-*cis*-9-Ethoxy-6-[4-(2-ethyl-2H-tetrazol-5-yl)phenyl]-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridine



C₂₅ H₂₉ N₅ O₂; Mol wt: 431.5371

ACTION – Agent for the treatment of airways disorders such as asthma and bronchitis, a selective inhibitor of phosphodiesterase type 4 (PDE4; -logIC₅₀ = 8.78). A representative compound from a series of tetrazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
272874	Me	H	C ₂₃ H ₂₅ N ₅ O ₂
272875	Me	4-MeO-PhCH ₂	C ₃₁ H ₃₃ N ₅ O ₃
272876	H	Et	C ₂₄ H ₂₇ N ₅ O ₂

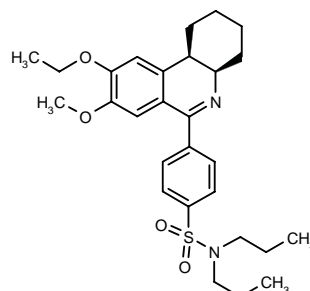
SOURCE – Byk Gulden.

REFERENCES

1. Amschler, H. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Novel tetrazole derivs*. WO 9905111.

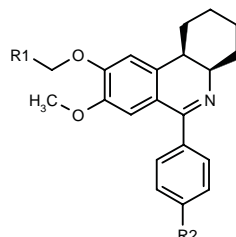
272877

(±)-*cis*-4-[9-Ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl]-N,N-dipropylbenzenesulfonamide



C₂₈ H₃₈ N₂ O₄ S; Mol wt: 498.6842

ACTION – Agent for the treatment of airways disorders such as asthma and bronchitis, a selective inhibitor of phosphodiesterase type 4 (PDE4; $-\log IC_{50} = 9.25$). A representative compound from a series of substituted 6-phenylphenanthridines, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
272878	Me	SO ₂ NH ₂	racemic	C ₂₂ H ₂₆ N ₂ O ₄ S
272879	Me	4-Me-PhNHSO ₂	racemic	C ₂₉ H ₃₂ N ₂ O ₄ S
272880	H	4-Me-PhNHSO ₂	(-)	C ₂₈ H ₃₀ N ₂ O ₄ S
272881	Me	3-Pyr-CONH	racemic	C ₂₈ H ₂₉ N ₃ O ₃

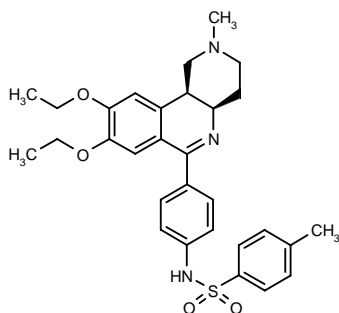
SOURCE – Byk Gulden.

REFERENCES

1. Amschler, H. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Subst. 6-phenylphenanthridines*. WO 9905113.

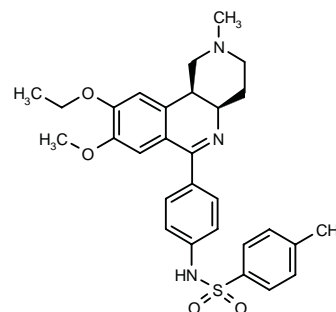
272895

(-)-*cis*-*N*-[4-(8,9-Diethoxy-2-methyl-1,2,3,4,4a,10b-hexahydrobenzo[*c*][1,6]naphthyridin-6-yl)phenyl]-4-methylbenzenesulfonamide



C₃₀ H₃₅ N₃ O₄ S; Mol wt: 533.6895

ACTION – Phosphodiesterase (PDE) type 3, 4 and 5 inhibitor, an analogue of tolafentrine with higher potency against PDE3, PDE4 and PDE5 *in vitro* ($-\log IC_{50} = 7.10$, 8.60 and 7.04, respectively, vs. 7.02, 7.20 and 5.63, respectively, for tolafentrine). Compound also inhibited the fMLP-stimulated formation of reactive oxygen species in human polymorphonuclear leukocytes ($-\log IC_{50} = 7.39$ vs. 6.07 for tolafentrine). Potentially useful in the treatment of airways disorders and hypertension and related disorders. Another specifically claimed analogue is:



272896: C₂₉ H₃₃ N₃ O₄ S

SOURCE – Byk Gulden.

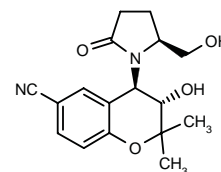
REFERENCES

1. Gutterer, B. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Benzonaphthyridine*. WO 9855481.

MJ-451

272665

(3*S*, 4*R*)-3-Hydroxy-4-[2(*S*)-(hydroxymethyl)-5-oxopyrrolidinyl]-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-carbonitrile



C₁₇ H₂₀ N₂ O₄; Mol wt: 316.3550

ACTION – Selective ATP-sensitive K⁺ channel (K_{ATP}) opener with potent relaxant activity in guinea pig airways smooth muscle. Compound antagonized carbachol- and histamine-induced contractions in isolated guinea pig trachea (pD₂ = 6.19 and 6.28, respectively), being approximately 5-fold less potent than the standard cromakalim. MJ-451 also inhibited guinea pig trachea contractions induced by low but not high KCl concentrations, indicating K⁺ channel-opening activity. The relaxant activity of the compound on carbachol-induced tracheal muscle contractions was antagonized by glibenclamide, but not by propranolol, a selective purinoceptor P1 receptor antagonist or charybdotoxin, demonstrating its selectivity for ATP-sensitive K⁺ channels.

SOURCE – National Taiwan University, Taipei (TW).

REFERENCES

1. Lin, C.H. et al. *Pharmacological characteristics of MJ-451, a new benzopyran-derived ATP-sensitive potassium channel opener, in guinea pig isolated trachea*. Pharmacology 1998, 57(6): 314.

NA-00226A

271964

ACTION – Compound isolated from *Streptomyces* sp. NA00226 (FERM-P-16196) that possesses cAMP-phosphodiesterase-inhibitory activity (IC₅₀ = 22 μM against enzyme from bovine tracheal smooth muscle).

SOURCE – Nippon Kayaku.

REFERENCES

1. Nishikiori, T. et al. (Nippon Kayaku Co., Ltd.) *Novel physiologically active substance NA00226A, its preparation method and use.* JP 98313886.

SALMETEROL XINAFOATE+/FLUTICASONE PROPIONATE++ New combination

271392

ACTION – Combination of the long-acting β₂-adrenoceptor agonist salmeterol xinafoate with proven efficacy as a long-acting bronchodilator, and the inhaled corticosteroid fluticasone propionate, which treats inflammation.

INDICATION – Regular treatment of asthma in adults and children in cases where the use of such a combination is deemed appropriate.

PRESENTATION – Predispensed inhalation powder containing salmeterol xinafoate equivalent to 50 μg salmeterol and 100, 250 or 500 μg fluticasone propionate.

PROPRIETARY NAMES – *Seretide Diskus* (SE); *Seretide Accuhaler* (GB).

SOURCE – Glaxo Wellcome.

RECENT REFERENCES

1. Bateman, E. et al. *Efficacy of a new combination of salmeterol and fluticasone propionate in patients with varying asthma severity.* Eur Respir J 1998, 12(Suppl. 29): Abst P163.
2. Johansson, G. et al. *Salmeterol/fluticasone propionate combination dry powder inhaler (50/100 mcg BID) is more effective than budesonide (400 mcg BID) in mild to moderate asthma.* Eur Respir J 1998, 12(Suppl. 29): Abst P162.
3. Pieters, W. et al. *A new inhaler combination containing salmeterol and fluticasone propionate is well-tolerated in longterm use.* Eur Respir J 1998, 12(Suppl. 29): Abst P164.
4. *First market introduction for new asthma treatment — Seretide Diskus.* DailyDrugNews.com (Daily Essentials) 1999, Feb 1.
5. *Glaxo Wellcome seeks U.S. regulatory approval for combination asthma treatment.* DailyDrugNews.com (Daily Essentials) 1999, March 30.
6. *New market introduction for Seretide.* DailyDrugNews.com (Daily Essentials) 1999, March 15.
7. *Seretide cleared for marketing in most E.U. countries.* DailyDrugNews.com (Daily Essentials) 1999, Jan 15.

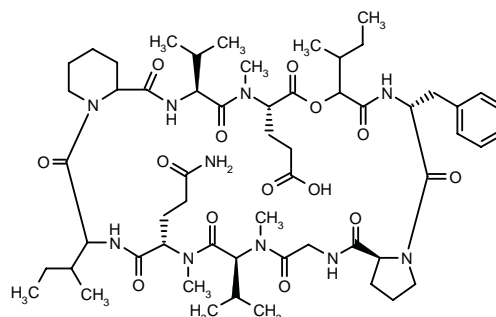
*Drug Data Reo 1991, 013(04): 0296.

**Drug Data Rep 1991, 013(02): 0113.

SCH-217048

272043

(6*R*,12*S*,15*S*,27*S*,30*S*,35*aS*)-6-Benzyl-27-(2-carbamoyl-ethyl)-12-(2-carboxyethyl)-15,30-diisopropyl-13,28,31-trimethyl-9,24-bis(1-methylpropyl)perhydropyrido-[1,2-*v*]pyrrolo[1,2-*g*]-10-oxa-4,7,13,16,22,25,28,31,34-nonaazacyclotriacontine-5,8,11,14,17,23,26,29,32,35-decanone



C57 H88 N10 O14; Mol wt: 1137.3780

White solid, m.p. 192-4 °C.

ACTION – Potent neurokinin (NK) receptor antagonist, a cyclodepsipeptide isolated from an unidentified fungal fermentation broth, with high selectivity for NK₂ receptors (IC₅₀ = 50 nM) over NK₁ receptors (IC₅₀ > 1000 nM).

SOURCE – Schering-Plough.

REFERENCES

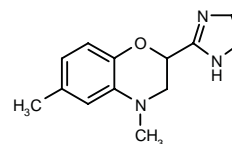
1. Hegde, V.R. et al. *Sch 217048: A novel cyclodepsipeptide with neurokinin antagonist activity.* J Org Chem 1998, 63(25): 9584.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

272291

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine



C13 H17 N3 O; Mol wt: 231.2973

ACTION – Antihypertensive agent with high affinity for the imidazoline receptors I₁ and I₂ (K_i = 22 and 2.0 nM, respectively). Antihypertensive activity was demonstrated in conscious and spontaneously hypertensive rats at a dose of 15 mg/kg p.o., as well as in anesthetized normotensive rabbits, and it is reported to have very low acute toxicity following oral administration in mice. Other specifically claimed substituted imidazoline derivatives include the following:

NA-00226A

271964

ACTION – Compound isolated from *Streptomyces* sp. NA00226 (FERM-P-16196) that possesses cAMP-phosphodiesterase-inhibitory activity (IC₅₀ = 22 μM against enzyme from bovine tracheal smooth muscle).

SOURCE – Nippon Kayaku.

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SALMETEROL XINAFOATE+/FLUTICASONE PROPIONATE++ New combination

271392

ACTION – Combination of the long-acting β₂-adrenoceptor agonist salmeterol xinafoate with proven efficacy as a long-acting bronchodilator, and the inhaled corticosteroid fluticasone propionate, which treats inflammation.

INDICATION – Regular treatment of asthma in adults and children in cases where the use of such a combination is deemed appropriate.

PRESENTATION – Predispensed inhalation powder containing salmeterol xinafoate equivalent to 50 μg salmeterol and 100, 250 or 500 μg fluticasone propionate.

PROPRIETARY NAMES – *Seretide Diskus* (SE); *Seretide Accuhaler* (GB).

SOURCE – Glaxo Wellcome.

RECENT REFERENCES

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3. Pieters, W. et al. *A new inhaler combination containing salmeterol and fluticasone propionate is well-tolerated in longterm use.* Eur Respir J 1998, 12(Suppl. 29): Abst P164.
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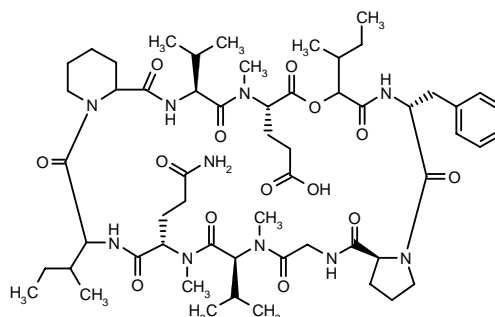
*Drug Data Reo 1991, 013(04): 0296.

**Drug Data Rep 1991, 013(02): 0113.

SCH-217048

272043

(6*R*,12*S*,15*S*,27*S*,30*S*,35*aS*)-6-Benzyl-27-(2-carbamoyl-ethyl)-12-(2-carboxyethyl)-15,30-diisopropyl-13,28,31-trimethyl-9,24-bis(1-methylpropyl)perhydropyrido-[1,2-*v*]pyrrolo[1,2-*g*]-10-oxa-4,7,13,16,22,25,28,31,34-nonaazacyclotriacontine-5,8,11,14,17,23,26,29,32,35-decanone



C₅₇ H₈₈ N₁₀ O₁₄; Mol wt: 1137.3780

White solid, m.p. 192-4 °C.

ACTION – Potent neurokinin (NK) receptor antagonist, a cyclodepsipeptide isolated from an unidentified fungal fermentation broth, with high selectivity for NK₂ receptors (IC₅₀ = 50 nM) over NK₁ receptors (IC₅₀ > 1000 nM).

SOURCE – Schering-Plough.

REFERENCES

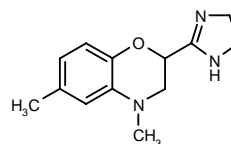
1. Hegde, V.R. et al. *Sch 217048: A novel cyclodepsipeptide with neurokinin antagonist activity.* J Org Chem 1998, 63(25): 9584.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

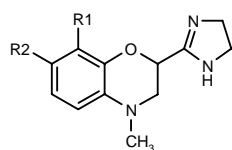
272291

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine



C₁₃ H₁₇ N₃ O; Mol wt: 231.2973

ACTION – Antihypertensive agent with high affinity for the imidazoline receptors I₁ and I₂ (K_i = 22 and 2.0 nM, respectively). Antihypertensive activity was demonstrated in conscious and spontaneously hypertensive rats at a dose of 15 mg/kg p.o., as well as in anesthetized normotensive rabbits, and it is reported to have very low acute toxicity following oral administration in mice. Other specifically claimed substituted imidazoline derivatives include the following:



Compound	R1	R2	Formula
272292	H	Me	C ₁₃ H ₁₇ N ₃ O
272293	Me	H	C ₁₃ H ₁₇ N ₃ O

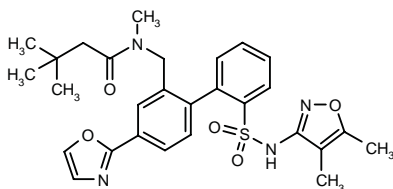
SOURCE – ADIR.

REFERENCES

1. Guillaumet, G. et al. (ADIR et Cie.) *Imidazolines substd. with a heterocyclic ring as α -2 antagonists*. EP 894796.

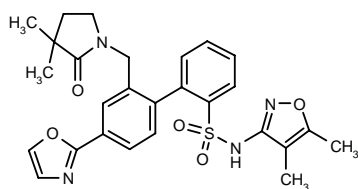
272888

N-[2'-(4,5-Dimethyl-3-isoxazolyl)sulfamoyl]-4-(2-oxazolyl)biphenyl-2-ylmethyl]-*N*,3,3-trimethylbutyramide



C28 H32 N4 O5 S; Mol wt: 536.6498

ACTION – Potent endothelin antagonist, as demonstrated by inhibition of the big ET-1 pressor response in rats following i.v. (ED₅₀ = 0.03 μ mol/kg) and p.o. administration, with a long duration of action (57 \pm 7 and 74 \pm 8% inhibition, respectively, at 15 and 195 min after a dose of 3 μ mol/kg p.o.). Compound exhibits an oral bioavailability of about 100% in rats and possesses good metabolic stability. Another specifically claimed compound is:



272889: C27 H28 N4 O5 S

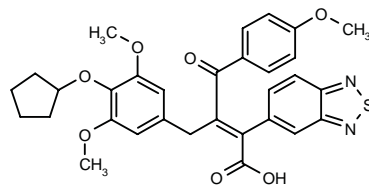
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Endothelin antagonists: N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl) [1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide and salts thereof*. WO 9833780.

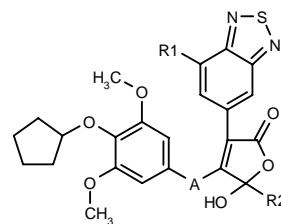
272940

2-(2,1,3-Benzothiadiazol-5-yl)-3-[4-(cyclopentyloxy)-3,5-dimethoxybenzyl]-4-(4-methoxyphenyl)-4-oxo-2-butenic acid

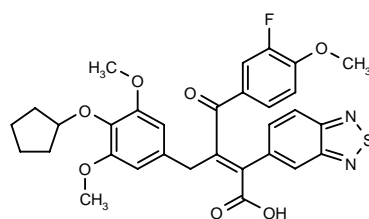


C31 H30 N2 O7 S; Mol wt: 574.6510

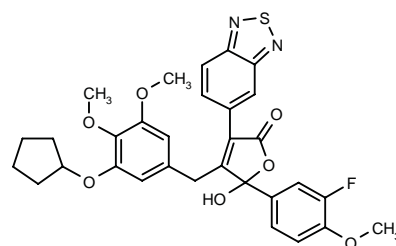
ACTION – Agent for the treatment of hypertension, heart failure, coronary disorders, renal, cerebral and myocardial ischemia, renal failure, stroke, subarachnoid hemorrhage, arteriosclerosis, pulmonary hypertension, inflammation, asthma, prostatic hyperplasia and endotoxic shock, an endothelin receptor antagonist with high affinity for ET_A and ET_B receptors. Other specifically claimed compounds within this series of benzothia(oxa)diazol derivatives include the following:



Compound	R1	R2	A	Formula
272942	H	4-MeO-Ph	bond	C ₃₀ H ₂₈ N ₂ O ₇ S
272943	H	3-F-4-MeO-Ph	bond	C ₃₀ H ₂₇ FN ₂ O ₇ S
272945	Me	3-F-4-MeO-PhCO	-CH2-	C ₃₃ H ₃₁ FN ₂ O ₈ S



272941: C31 H29 F N2 O7 S



272944: C31 H29 F N2 O7 S

SOURCE – Merck KGaA.

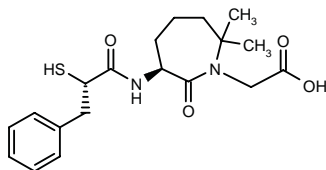
REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Benzothia(oxa)diazol derivs. and their use as endothelin-receptor antagonists*. WO 9905132.

BMS-189921

235519

2-[2,2-Dimethyl-7-oxo-6(*S*)-[3-phenyl-2(*S*)-sulfanyl-propanamido]hexahydro-1*H*-azepin-1-yl]acetic acid



C19 H26 N2 O4 S; Mol wt: 378.4904

ACTION – Antihypertensive agent, a dual competitive inhibitor of angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP), with K_i values of 5.3 and 16 nM, respectively, against rabbit lung ACE and rat kidney NEP (IC_{50} = 12 and 63 nM, respectively), showing comparable potency to the reference compound omapatrilat (K_i ACE = 6.0 nM; K_i NEP = 8.9 nM). In conscious normotensive rats, it exhibited high oral efficacy in inhibiting the angiotensin I-induced pressor response, with an ED_{50} of 0.6 μ mol/kg (i.v. ED_{50} = 0.1 μ mol/kg). In spontaneously hypertensive rats (SHR), compound given orally for 9 days at a dose of 100 μ mol/kg induced a progressive decrease in mean arterial blood pressure, with a maximum reduction of 30 mmHg, and this effect was comparable to that of omapatrilat. In 1-kidney DOCA/salt hypertensive rats, at a dose of 100 μ mol/kg/day p.o. for 4 days it decreased systolic blood pressure by about 60 mmHg, with a rapid onset of action. BMS-189921 is presently in phase II clinical studies for the treatment of hypertension and congestive heart failure; preliminary results from clinical studies demonstrated a favorable safety and clinical efficacy profile.

SOURCE – Bristol-Myers Squibb.

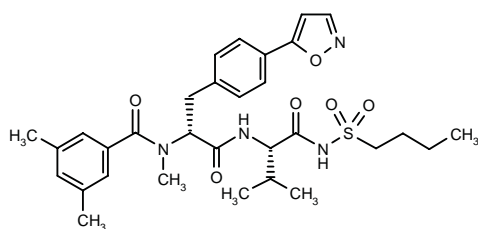
REFERENCES

1. Karanewsky, D.S. et al. (Bristol-Myers Squibb Co.) *Dual action inhibitors*. EP 599444, US 5552397.
2. Robl, J.A. et al. *Vasopeptidase inhibitors: Incorporation of geminal and spirocyclic substituted azepinones in mercaptoacyl dipeptides*. J Med Chem 1999, 42(2): 305.
3. Bristol-Myers Squibb Co. Annual Report 1995.

IRL-3630^{*,1-3}

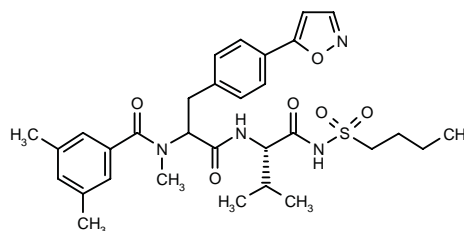
250585

*N*¹-(Butylsulfonyl)-*N*²-[*N*-(3,5-dimethylbenzoyl)-*N*-methyl-4-(5-isoxazolyl)-D-phenylalanyl]-L-valinamide



C31 H40 N4 O6 S; Mol wt: 596.7450

ACTION – Highly potent dual endothelin ET_A and ET_B receptor antagonist with K_i values of 1.5 and 1.2 nM for human ET_A and ET_B receptors, respectively, expressed in CHO cells, the most potent enantiomer of **IRL-3461**.



IRL-3461 [231803]^{,1-4}**: C31 H40 N4 O6 S

SOURCE – Novartis.

REFERENCES

1. Fröh, T. et al. (Novartis Japan KK) *Antagonists of endothelin receptors*. EP 753004, JP 97510720, US 5703106, WO 9526360.
2. Sakaki, J. et al. (Novartis Japan KK) *Antagonists of endothelin receptors*. WO 9711960.
3. Sakaki, J. et al. *Stereoselective synthesis of a novel bisfunctional endothelin antagonist, IRL-3630*. Bioorg Med Chem Lett 1998, 8(16): 2247.
4. Sakaki, J. et al. *Discovery of IRL-3461: A novel and potent endothelin antagonist with balanced ET_A/ET_B affinity*. Bioorg Med Chem Lett 1998, 8(16): 2241.

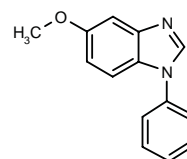
*Identified compound **250585** Drug Data Report 1997, 019(09): 0795.

Identified compound **231803 (see **229520**) Drug Data Report 1996, 018(03): 0237.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

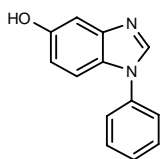
271578

5-Methoxy-1-phenyl-1*H*-benzimidazole



C14 H12 N2 O; Mol wt: 224.2618

ACTION – A potent and selective ATP-site inhibitor of platelet-derived growth factor (PDGF) receptor (IC_{50} = 0.43 μ M for inhibition of phosphorylation in transfected SF9 cells overexpressing the PDGF receptor protein) with high selectivity (about 50-fold) over the fibroblast growth factor (FGF) receptor (IC_{50} = 22 μ M for inhibition of phosphorylation in cells overexpressing the FGF receptor protein). Compound was a moderately effective inhibitor of PDGF-stimulated PDGF receptor autophosphorylation in rat aorta smooth muscle cells (IC_{50} = 1.9 μ M). Potentially useful for the prevention of restenosis following vascular interventions, as well as for use as an anticancer agent. Another 1-phenylbenzimidazole is:



271579: C₁₃ H₁₀ N₂ O

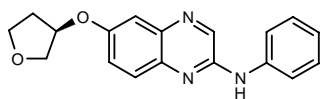
SOURCE – Warner-Lambert.

REFERENCES

1. Palmer, B.D. et al. *Structure-activity relationships for 1-phenylbenzimidazoles as selective ATP site inhibitors of the platelet-derived growth factor receptor.* J Med Chem 1998, 41(27): 5457.

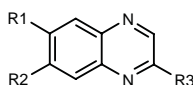
272081

N-Phenyl-*N*-[6-[tetrahydro-3(*R*)-furanyloxy]quinoxalin-2-yl]amine



C₁₈ H₁₇ N₃ O₂; Mol wt: 307.3513

ACTION – Antiproliferative agent for the treatment of restenosis, a protein tyrosine kinase inhibitor particularly active against platelet-derived growth factor (PDGF) receptor and p56^{lck} (Lck) tyrosine kinases. A compound within a series of specifically claimed quinoline and quinoxaline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
272082	OEt	OEt	(S)-NHCH(Me)Ph	C ₂₀ H ₂₃ N ₃ O ₂
272083	OMe	H	3-Me-PhNH	C ₁₆ H ₁₅ N ₃ O
272084	OEt	OEt	4-F-PhNH	C ₁₈ H ₁₈ FN ₃ O ₂
272085	OEt	OEt	OPh	C ₁₈ H ₁₈ N ₂ O ₃
272086	OMe	OMe	3-Cl-PhNH	C ₁₆ H ₁₄ ClN ₃ O ₂

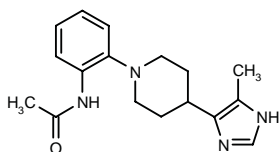
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Myers, M. et al. (Rhône-Poulenc Rorer Pharmaceuticals Inc.) *Quinoline and quinoxaline cpds. which inhibit platelet-derived growth factor and/or P56^{lck} tyrosine kinases.* WO 9854156, WO 9854157, WO 9854158.

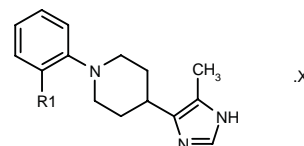
272224

N-[2-[4-(5-Methyl-1*H*-imidazol-4-yl)-1-piperidinyl]-phenyl]acetamide



C₁₇ H₂₂ N₄ O; Mol wt: 298.3878

ACTION – An inhibitor of Na⁺/H⁺ exchange with potential in the treatment of arterial and pulmonary hypertension, cardiac arrhythmia, cardiac ischemia, myocardial infarction, heart failure, angina pectoris, peripheral organ and CNS ischemic disorders, nephropathy, edema, fibrosis and cancer, as well as cardiac and vascular hyperplasia or hypertrophy. Within this series of 4-(1*H*-imidazol-4-yl)piperidine derivatives, the following are also included:



Compound	R1	X	Formula
272225	NH2		C ₁₅ H ₂₀ N ₄
272226	NHCOCH=CHPh		C ₂₄ H ₂₆ N ₄ O
272227	i-BuOCONH		C ₂₀ H ₂₈ N ₄ O ₂
272228	NHCONHEt		C ₁₈ H ₂₅ N ₅ O
272229	NHSO ₂ Me		C ₁₆ H ₂₂ N ₄ O ₂ S
272230	NHCOPr		C ₁₉ H ₂₆ N ₄ O
272231	N(Me)COPr	fumarate	C ₂₀ H ₂₈ N ₄ O.C ₄ H ₄ O ₄
272232	NHCH2Ph		C ₂₂ H ₂₆ N ₄
272233	NHCH2OMe		C ₁₇ H ₂₄ N ₄ O
272234	NHCOCH2N(Me) ₂		C ₁₉ H ₂₇ N ₅ O
272235	2-oxo-1-pyrrolidinyl	fumarate	C ₁₉ H ₂₄ N ₄ O.C ₄ H ₄ O ₄

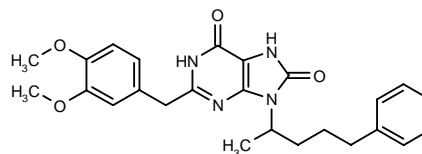
SOURCE – Synthélabo.

REFERENCES

1. Cremer, G. and Hoornaert, C. (Synthélabo) *(1*H*-Imidazol-4-yl)piperidine derivs., preparation and application in therapy.* WO 9901435.

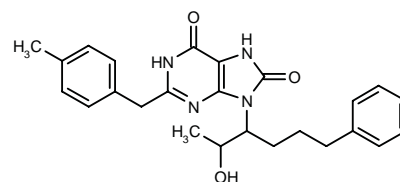
272882

2-(3,4-Dimethoxybenzyl)-9-(1-methyl-4-phenylbutyl)-6,7,8,9-tetrahydro-1*H*-purine-6,8-dione



C₂₅ H₂₈ N₄ O₄; Mol wt: 448.5202

ACTION – Agent for the treatment of cardiovascular and cerebrovascular diseases, as well as peripheral vascular diseases and diseases of the urogenital tract, a phosphodiesterase (PDE) inhibitor with selectivity for PDE3 (IC₅₀ = 500 nM) over PDE2 (IC₅₀ = 1000 nM) and PDE5 (IC₅₀ > 1000 nM). Another compound from this series of cyclic urea derivatives is:



272884: C₂₅ H₂₈ N₄ O₃

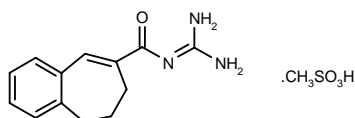
SOURCE – Bayer.

REFERENCES

1. Rosentreter, U. et al. (Bayer AG) *Purine diones as phosphodiesterase inhibitors*. WO 9832755.

272898

*N*²-(6,7-Dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)guanidine methanesulfonate



C13 H15 N3 O . C H4 O3 S; Mol wt: 325.3871

ACTION – An inhibitor of cellular Na⁺/H⁺ exchange ($K_i < 0.1 \mu\text{M}$ in rat thymocytes) with potential in the treatment of cardiovascular disorders such as hypertension, angina pectoris, myocardial infarction, heart failure and arrhythmias, cerebrovascular disorders such as stroke and edema, renal diseases such as diabetic nephropathy, arteriosclerosis, shock states and hyperlipidemia.

SOURCE – Fujisawa.

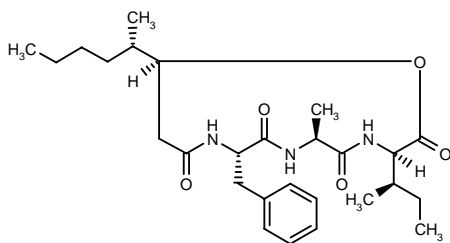
REFERENCES

1. Takenaka, K. and Inoue, Y. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidine derivs. as inhibitors of Na⁺/H⁺ exchange in cells*. WO 9855475.

BEAUVERIOLIDE III^{2,3}

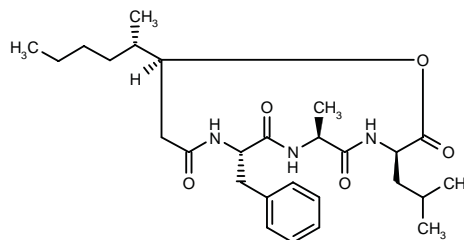
271858

(3*R*,6*S*,9*S*,13*S*)-9-Benzyl-6-methyl-13-[1(*S*)-methylpentyl]-3-[1(*R*)-methylpropyl]-1-oxa-4,7,10-triazacyclotridecane-2,5,8,11-tetraone



C27 H41 N3 O5; Mol wt: 487.6369

ACTION – Inhibitor of macrophage-derived foam cell formation extracted from the fermentation broth of *Beauveria* sp. FO-6979, proven to concentration-dependently (3-10 μM) decrease the size and the number of lipid droplets in macrophages without cytotoxic effects on macrophages (up to 20 μM). Compound was devoid of antimicrobial activity against a range of Gram-positive and Gram-negative bacteria. In preliminary experiments, it appeared to inhibit cholesteryl ester synthesis. Potentially useful in the treatment or prevention of atherosclerosis. Another related compound is:



Beauveriolide I [271860]¹⁻³: C27 H41 N3 O5

SOURCES – Kitasato Institute, Tokyo (JP); Kitasato University, Tokyo (JP).

REFERENCES

1. Mochizuki, K. et al. *The structures of bioactive cyclodepsipeptides, beauveriolides I and II, metabolites of entomopathogenic fungi Beauveria sp.* Bull Chem Soc Jpn 1993, 66(10): 3041.

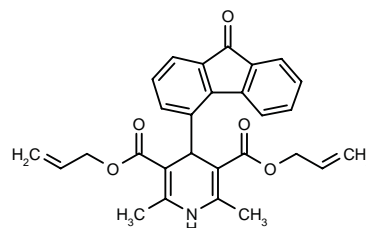
2. Namatame, I. et al. *Beauveriolides, specific inhibitors of lipid droplet formation in mouse macrophages, produced by Beauveria sp. FO-6979*. J Antibiot 1999, 52(1): 1.

3. Namatame, I. et al. *Structure elucidation of fungal beauveriolide III, a novel inhibitor of lipid droplet formation in mouse macrophages*. J Antibiot 1999, 52(1): 7.

FLUODIPINE

271795

2,6-Dimethyl-4-(9-oxo-9*H*-fluoren-4-yl)-1,4-dihydropyridine-3,5-dicarboxylic acid bis(2-propenyl) diester



C28 H25 N O5; Mol wt: 455.5075

M.p. 201-4 °C.

ACTION – Cardiodepressant, a 1,4-dihydropyridine derivative with similar cardiodepressant effect and lower inhibitory activity on vascular contraction than the standard nifedipine. Compound showed higher affinity for cardiac ($K_i = 2.57 \text{ nM}$ against [³H]-isradipine) than for vascular L-type Ca²⁺ channels ($\text{IC}_{50} = 792 \text{ nM}$ for inhibition of KCl-stimulated Ca²⁺ influx in vascular smooth muscle cells). It exhibited significant species differences in tissue selectivity: the most selective cardiodepressant activity was observed in guinea pig atrial preparations (chronotropic and inotropic $\text{EC}_{50} = 20$ and 96 nM , respectively, vs. $\text{IC}_{50} = 1400 \text{ nM}$ for inhibition of K⁺-stimulated aorta contractions), where compound was 2-3 times more active than nifedipine. *In vivo* in anesthetized rabbits, it produced a dose-related bradycardic response ($\text{ID}_{25} = 8.5 \text{ mg/kg i.v.}$) that was rapid in onset and short in duration, without significantly affecting mean arterial blood pressure; in contrast, nifedipine significantly reduced mean arterial pressure without significantly altering heart rate. Fluodipine (10 mg/kg i.v.) was also shown to significantly reduce heart rate in conscious rabbits. Potentially useful for the treatment of ischemic heart disease, in particular for patients in whom β -blockade is contraindicated.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Università degli Studi di Milano, Milano (IT).

REFERENCES

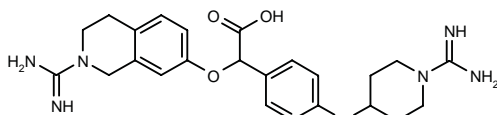
1. Budriesi, R. et al. *Selective cardiodepressant activity of fluodipine, a fluorenone-1,4-dihydropyridine derivative*. Eur J Pharmacol 1998, 359(2-3): 161.
2. Caccamese, S. et al. *Fluorenone 1,4-dihydropyridine derivatives with cardiodepressant activity: Enantiomeric separation by chiral HPLC and conformational aspects*. Chirality 1996, 8(3): 281.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

270819

2-(2-Amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)-2-[4-(1-amidino-4-piperidinyloxy)phenyl]acetic acid dihydrochloride

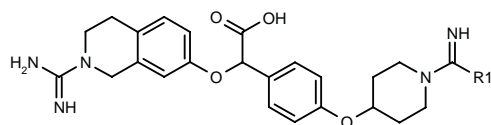


.2HCl

C₂₄ H₃₀ N₆ O₄ . 2HCl; Mol wt: 539.4608

White solid, m.p. 95 °C.

ACTION – Anticoagulant, a potent and selective inhibitor of factor Xa with a K_i of 0.044 μ M; it did not inhibit thrombin or plasmin (K_i > 100 and 44 μ M, respectively) and showed relatively weak activity against trypsin (K_i = 0.2 μ M). Compound exhibited anticoagulant activity in human blood, prolonging the partial thromboplastin time (aPTT) but not the thrombin time (TT), with ED₂₀₀ values (concentrations doubling aPTT or TT) of 9 and > 500 μ M, respectively. Other related compounds from this series of tetrahydroisoquinoline-based molecules include the following:



.2HCl

Compound	R1	Formula
270820	4-MeO-Ph	C ₃₁ H ₃₅ N ₅ O ₅ .2HCl
272022	Me	C ₂₅ H ₃₁ N ₅ O ₄ .2HCl

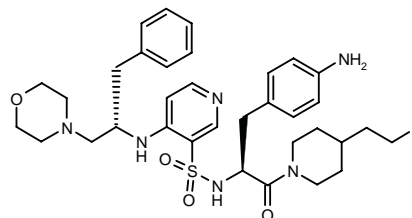
SOURCE – Roche.

REFERENCES

1. Kucznierz, R. et al. (Boehringer Mannheim GmbH) *New cyclic guanidines, process for preparing the same and medicaments*. DE 19530996, EP 846115, WO 9708165.
2. Kucznierz, R. et al. *Tetrahydro-isoquinoline-based factor Xa inhibitors*. J Med Chem 1998, 41(25): 4983.

271193

N-[1(*S*)-(4-Aminobenzyl)-2-[4-(2-fluoroethyl)-1-piperidinyl]-2-oxoethyl]-4-[1(*S*)-benzyl-2-(4-morpholinyl)-ethylamino]pyridine-3-sulfonamide



C₃₄ H₄₅ F N₆ O₄ S; Mol wt: 652.8315

ACTION – Orally active thrombin inhibitor (K_i = 22 nM against human thrombin) derived from CGH-1668, with the same potency as the parent compound but improved oral pharmacokinetics in rats, giving an absolute bioavailability of 61% after administration of 10 mg/kg p.o.

SOURCE – Novartis.

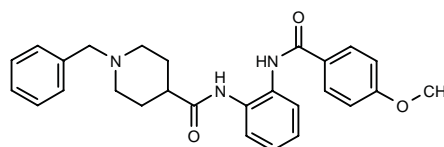
REFERENCES

1. Brundish, D.E. et al. (Ciba-Geigy AG) *Thrombin inhibitors*. WO 9746553.
2. Ambler, J. et al. *The discovery of orally available thrombin inhibitors: Studies towards the optimisation of CGH1668*. Bioorg Med Chem Lett 1998, 8(24): 3583.

272281

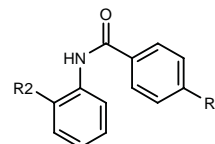
1-Benzyl-*N*-[2-(4-methoxybenzamido)phenyl]piperidine-4-carboxamide

N-[2-(1-Benzylpiperidin-4-ylcarboxamido)phenyl]-4-methoxybenzamide



C₂₇ H₂₉ N₃ O₃; Mol wt: 443.5441

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa. Other exemplified compounds include the following:



Compound	R1	R2	Formula
272282	OMe	5-Br-1,3-dioxo-2H-2-isindolyl	C ₂₂ H ₁₅ BrN ₂ O ₄
272283	Ac	4-MeO-PhNHCO	C ₂₃ H ₂₀ N ₂ O ₄
272284	OMe	3-NH2-4-MeO-PhCONH	C ₂₂ H ₂₁ N ₃ O ₄

SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9900121.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Università degli Studi di Milano, Milano (IT).

REFERENCES

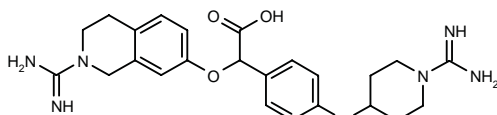
1. Budriesi, R. et al. *Selective cardiodepressant activity of fluodipine, a fluorenone-1,4-dihydropyridine derivative*. Eur J Pharmacol 1998, 359(2-3): 161.
2. Caccamese, S. et al. *Fluorenone 1,4-dihydropyridine derivatives with cardiodepressant activity: Enantiomeric separation by chiral HPLC and conformational aspects*. Chirality 1996, 8(3): 281.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

270819

2-(2-Amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)-2-[4-(1-amidino-4-piperidinyloxy)phenyl]acetic acid dihydrochloride

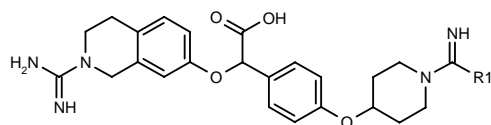


.2HCl

C₂₄ H₃₀ N₆ O₄ . 2HCl; Mol wt: 539.4608

White solid, m.p. 95 °C.

ACTION – Anticoagulant, a potent and selective inhibitor of factor Xa with a K_i of 0.044 μ M; it did not inhibit thrombin or plasmin (K_i > 100 and 44 μ M, respectively) and showed relatively weak activity against trypsin (K_i = 0.2 μ M). Compound exhibited anticoagulant activity in human blood, prolonging the partial thromboplastin time (aPTT) but not the thrombin time (TT), with ED₂₀₀ values (concentrations doubling aPTT or TT) of 9 and > 500 μ M, respectively. Other related compounds from this series of tetrahydroisoquinoline-based molecules include the following:



.2HCl

Compound	R1	Formula
270820	4-MeO-Ph	C ₃₁ H ₃₅ N ₅ O ₅ .2HCl
272022	Me	C ₂₅ H ₃₁ N ₅ O ₄ .2HCl

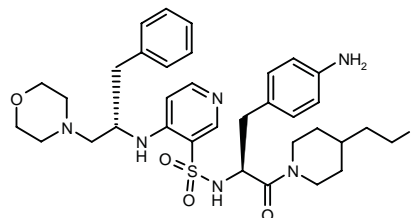
SOURCE – Roche.

REFERENCES

1. Kucznierz, R. et al. (Boehringer Mannheim GmbH) *New cyclic guanidines, process for preparing the same and medicaments*. DE 19530996, EP 846115, WO 9708165.
2. Kucznierz, R. et al. *Tetrahydro-isoquinoline-based factor Xa inhibitors*. J Med Chem 1998, 41(25): 4983.

271193

N-[1(*S*)-(4-Aminobenzyl)-2-[4-(2-fluoroethyl)-1-piperidinyl]-2-oxoethyl]-4-[1(*S*)-benzyl-2-(4-morpholinyl)-ethylamino]pyridine-3-sulfonamide



C₃₄ H₄₅ F N₆ O₄ S; Mol wt: 652.8315

ACTION – Orally active thrombin inhibitor (K_i = 22 nM against human thrombin) derived from CGH-1668, with the same potency as the parent compound but improved oral pharmacokinetics in rats, giving an absolute bioavailability of 61% after administration of 10 mg/kg p.o.

SOURCE – Novartis.

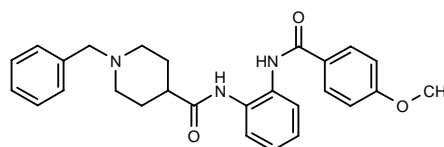
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1. Brundish, D.E. et al. (Ciba-Geigy AG) *Thrombin inhibitors*. WO 9746553.
2. Ambler, J. et al. *The discovery of orally available thrombin inhibitors: Studies towards the optimisation of CGH1668*. Bioorg Med Chem Lett 1998, 8(24): 3583.

272281

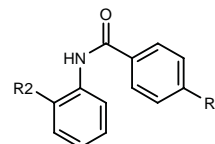
1-Benzyl-*N*-[2-(4-methoxybenzamido)phenyl]piperidine-4-carboxamide

N-[2-(1-Benzylpiperidin-4-ylcarboxamido)phenyl]-4-methoxybenzamide



C₂₇ H₂₉ N₃ O₃; Mol wt: 443.5441

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa. Other exemplified compounds include the following:



Compound	R1	R2	Formula
272282	OMe	5-Br-1,3-dioxo-2H-2-isindolyl	C ₂₂ H ₁₅ BrN ₂ O ₄
272283	Ac	4-MeO-PhNHCO	C ₂₃ H ₂₀ N ₂ O ₄
272284	OMe	3-NH2-4-MeO-PhCONH	C ₂₂ H ₂₁ N ₃ O ₄

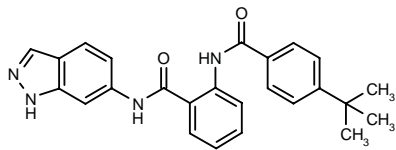
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9900121.

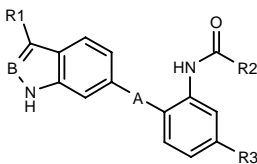
272285

2-(4-*tert*-Butylbenzamido)-*N*-(1*H*-indazol-6-yl)benzamide



C25 H24 N4 O2; Mol wt: 412.4906

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of factor Xa. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	Formula
272287	H	4-EtO-Ph	H	-NHCO-	N	C ₂₃ H ₂₀ N ₄ O ₃
272288	Cl	4- <i>t</i> -Bu-Ph	OH	-CONH-	CH	C ₂₈ H ₂₄ ClN ₃ O ₃
272289	H	1-(4-Pyr)-4-Pip	H	-NHCO-	N	C ₂₅ H ₂₄ N ₆ O ₂

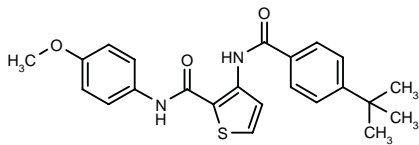
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 9900128.

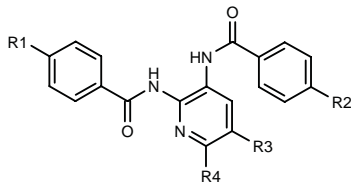
272299

3-(4-*tert*-Butylbenzamido)-*N*-(4-methoxyphenyl)-2-thiophenecarboxamide

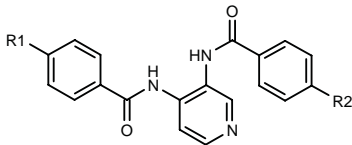


C23 H24 N2 O3 S; Mol wt: 408.5196

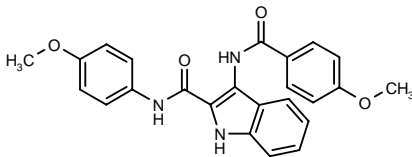
ACTION – Anticoagulant and antithrombotic agent with factor Xa-inhibitory activity. Other heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
272300	OMe	<i>t</i> -Bu	H	H	C ₂₄ H ₂₅ N ₃ O ₃
272303	<i>t</i> -Bu	OMe	H	H	C ₂₄ H ₂₅ N ₃ O ₃
272305	OMe	OMe	Br	Me	C ₂₂ H ₂₀ BrN ₃ O ₄
272307	OMe	OMe	H	H	C ₂₁ H ₁₉ N ₃ O ₄



Compound	R1	R2	Formula
272301	<i>t</i> -Bu	OMe	C ₂₄ H ₂₅ N ₃ O ₃
272302	OMe	<i>t</i> -Bu	C ₂₄ H ₂₅ N ₃ O ₃
272304	OMe	4-Pyr	C ₂₅ H ₂₀ N ₄ O ₃
272306	OMe	OMe	C ₂₁ H ₁₉ N ₃ O ₄
272309	N(Me) ₂	OMe	C ₂₂ H ₂₂ N ₄ O ₃



272308: C24 H21 N3 O4

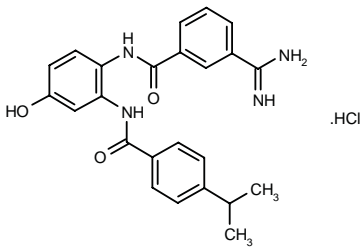
SOURCE – Lilly.

REFERENCES

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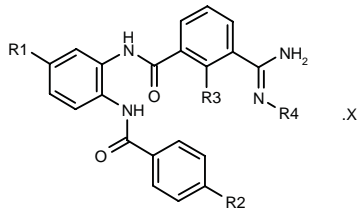
272344

3-Amidino-*N*-[4-hydroxy-2-(4-isopropylbenzamido)-phenyl]benzamide hydrochloride

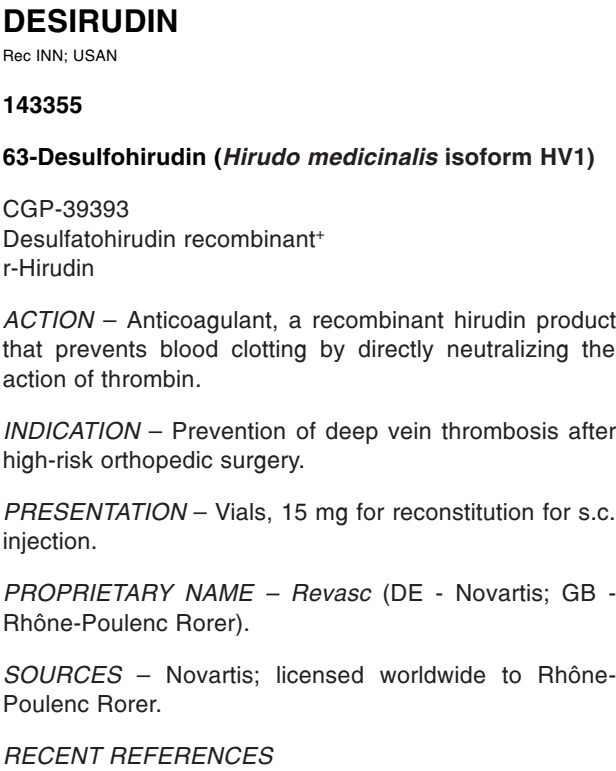
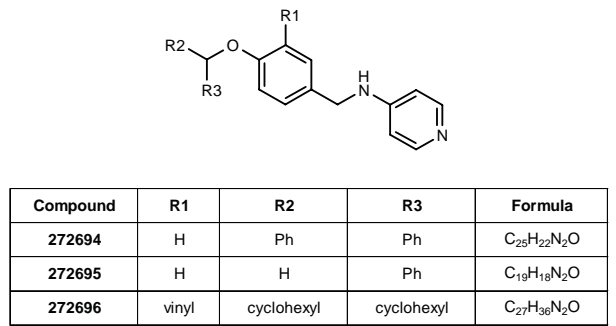
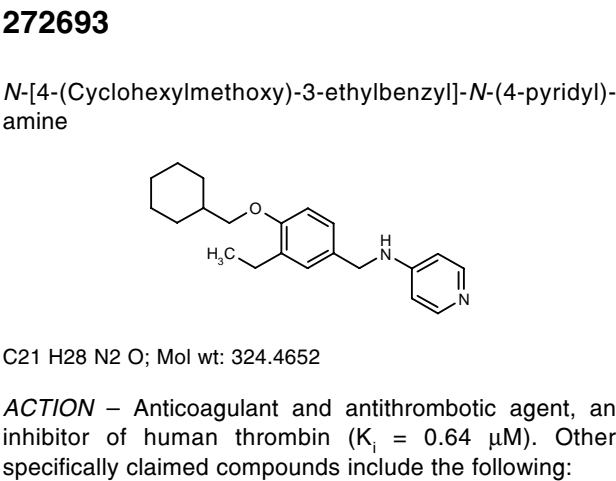
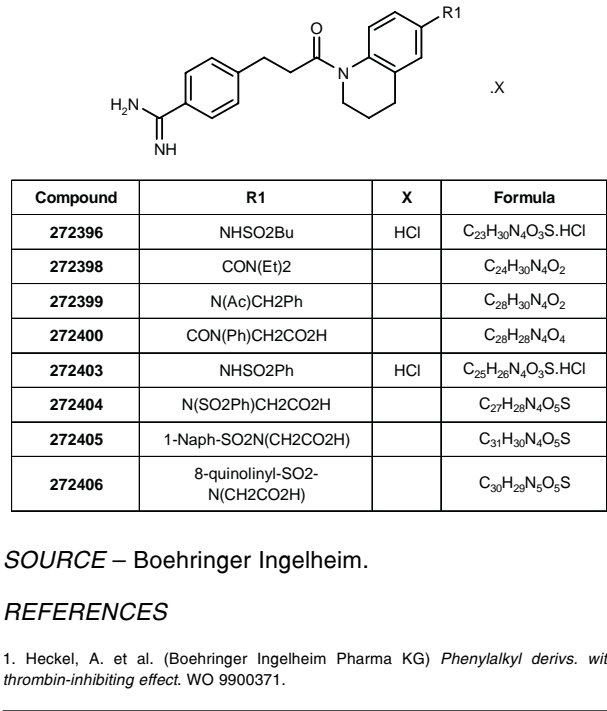
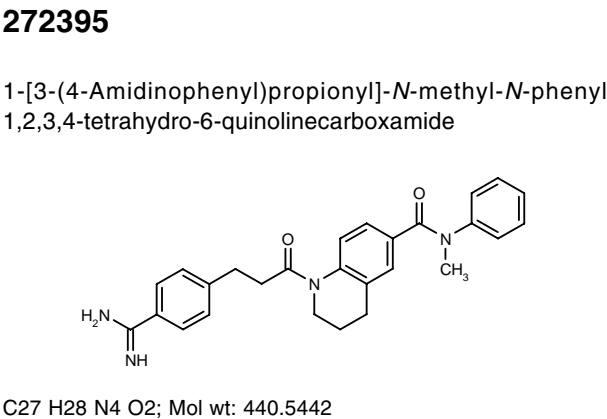
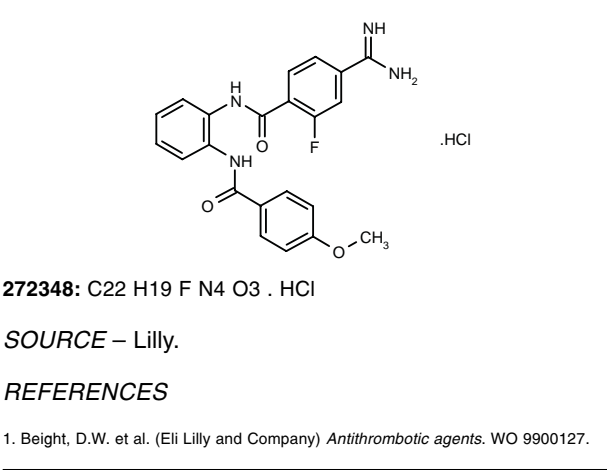


C24 H24 N4 O3 . HCl; Mol wt: 452.9395

ACTION – Anticoagulant and antithrombotic agent, an orally active and selective inhibitor of factor Xa proven active *in vivo* in models of thrombosis (arteriovenous shunt model in rats, FeCl₃ model of arterial injury in rats, canine model of coronary artery thrombosis). Other representative compounds include the following:



Compound	R1	R2	R3	R4	X	Formula
272346	H	OMe	H	OH		C ₂₂ H ₂₀ N ₄ O ₄
272347	H	OMe	H	H	HCl	C ₂₂ H ₂₀ N ₄ O ₃ .HCl
272349	CO ₂ H	<i>t</i> -Bu	H	H	HCl	C ₂₆ H ₂₆ N ₄ O ₄ .HCl
272350	H	OMe	OH	H	HCl	C ₂₂ H ₂₀ N ₄ O ₄ .HCl



3. Chorda, C. et al. *Comparison of the effects of unfractionated heparin, low molecular weight heparin and hirudin (Revasc™) on the fibrinolytic potential of cultured human umbilical vein endothelial cells.* Fibrinolysis 1996, 10(1): 43.

4. Ekman, S. et al. *Optimal dose-finding of recombinant hirudin, CGP 39393,desirudin ((TM) Revasc), in patients undergoing total hip replacement.* Thromb Haemost 1997, Suppl.: Abst PS-2012.

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9. Gertz, S.D. et al. *Hirudin reduces tissue factor expression in neointima after balloon injury in rabbit femoral and porcine coronary arteries.* Circulation 1998, 98(6): 580.

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12. Lefèvre, G. et al. *Effect of renal impairment on the pharmacokinetics and pharmacodynamics of desirudin.* Clin Pharmacol Ther 1997, 62(1): 50.

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18. Rao, K.A. et al. *Distinct effects of recombinant desulfatohirudin (Revasc) and heparin on plasma levels of fibrinopeptide A and prothrombin fragment F1.2 in unstable angina. A multicenter trial.* Circulation 1996, 94(10): 2389.

19. The TIMI 9 Investigators *Hirudin (TM)Revasc vs heparin after thrombolysis in acute myocardial infarction: Preliminary results from the TIMI 9B study.* Heart 1996, 75(5, Suppl. 1): Abst 171.

20. *Another European market opens up to desirudin.* DailyDrugNews.com (Daily Essentials) 1999, Feb 18.

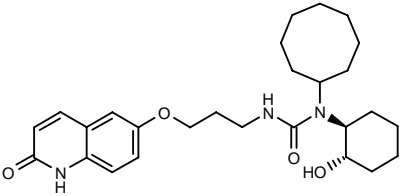
21. *First launch for Novartis anticoagulant takes place in Germany.* DailyDrugNews.com (Daily Essentials) 1998, Dec 15.

*Drug Data Report 1988, 010(08): 0647.

ANTIPLATELET THERAPY

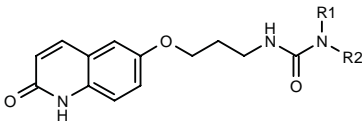
272055

trans-N-Cyclooctyl-N-(2-hydroxycyclohexyl)-N'-[3-(2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]urea



C27 H39 N3 O4; Mol wt: 469.6221

ACTION – Antithrombotic agent. a platelet aggregation inhibitor with IC₅₀ values of 0.08 and 0.03 μM, respectively, against ADP- and collagen-induced rabbit platelet aggregation. Compound was very potent *in vivo*, providing complete protection against pulmonary embolism elicited by collagen in mice at a dose of 30 mg/kg p.o. In addition, test compound was a potent *in vitro* inhibitor of phosphodiesterase type 3 (PDE3; IC₅₀ = 0.647 nM using recombinant enzyme). Certain compounds within the scope of the invention showed significant activity in inhibiting vascular intimal hypertrophy in rats caused by balloon injury of the left common artery. Other representative compounds include the following:



Compound	R1	R2	Formula
272056	cyclopropyl	(1R,2R)-2-OH-cyclohexyl	C ₂₂ H ₂₉ N ₃ O ₄
272059	cycloheptyl	trans-2-OH-cyclohexyl	C ₂₈ H ₃₇ N ₃ O ₄
272061	cyclohexyl	CH ₂ CH(Et)OEt	C ₂₈ H ₃₇ N ₃ O ₄
272062	H	cyclohexyl-N(Me)	C ₂₀ H ₂₈ N ₄ O ₃
272063	H	N(cyclopropyl)(cyclohexyl)	C ₂₂ H ₃₀ N ₄ O ₃

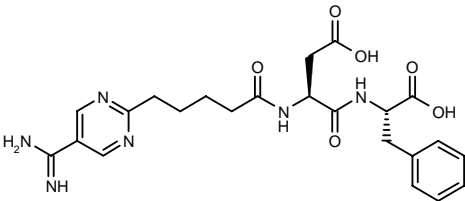
SOURCE – Otsuka.

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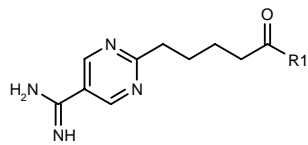
272710

N-[5-(5-Amidinopyrimidin-2-yl)pentanoyl]-L-aspartyl-L-phenylalanine



C23 H28 N6 O6; Mol wt: 484.5102

ACTION – Platelet aggregation inhibitor proven to inhibit ADP-induced aggregation of dog platelet-rich plasma (PRP) with an IC₅₀ value of 0.11 µM. Within this series of pyrimidinylamidino β-amino acid derivatives, the following compounds are also specifically claimed:



Compound	R1	Formula
272711	-L-Asp-L-Phe-NH2	C ₂₃ H ₂₉ N ₇ O ₅
272712	NHCH(Ph)CH ₂ CO ₂ H	C ₁₉ H ₂₃ N ₅ O ₃
272713	NHCH ₂ CH ₂ CO ₂ H	C ₁₃ H ₁₉ N ₅ O ₃
272714	NHCH ₂ CH ₂ CO ₂ Et	C ₁₅ H ₂₃ N ₅ O ₃
272715	NHCH(3-Pyr)CH ₂ CO ₂ H	C ₁₈ H ₂₂ N ₆ O ₃
272716	1,3-benzodioxol-5-yl- -CH(CH ₂ CO ₂ H)NH	C ₂₀ H ₂₃ N ₅ O ₅

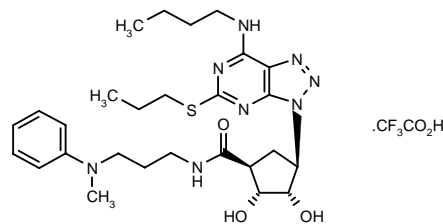
SOURCE – Monsanto.

REFERENCES

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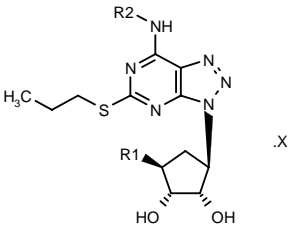
272995

(1*S*,2*R*,3*S*,4*R*)-4-[7-(Butylamino)-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxy-*N*-[3-(*N*-methyl-*N*-phenylamino)propyl]cyclopentane-1-carboxamide trifluoroacetate



C₂₇ H₄₀ N₈ O₃ S . C₂ H F₃ O₂; Mol wt: 670.7539

ACTION – Antithrombotic agent with P2T purinoceptor-antagonist activity, claimed for the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and angina. Other specifically claimed compounds within this series of triazolo[4,5-*d*]pyrimidines include the following:



Compound	R1	R2	X	Formula
272996	CONH-(CH ₂) ₃ NH ₂	Bu	CF ₃ CO ₂ H	C ₂₀ H ₃₄ N ₈ O ₃ S .C ₂ H ₃ F ₃ O ₂
272997	trans-4-NH ₂ - -cyclohexyl-NHCO	trans-2-Ph- -cyclopropyl	2CF ₃ CO ₂ H	C ₂₈ H ₃₈ N ₈ O ₃ S .2C ₂ H ₃ F ₃ O ₂
272999	CH ₂ NH ₂	Bu		C ₁₇ H ₂₉ N ₇ O ₂ S
273000	NH ₂	trans-2-Ph- -cyclopropyl		C ₂₁ H ₂₇ N ₇ O ₂ S
273001	(<i>E</i>)-CH=CH- CH ₂ NH ₂	trans-2-Ph- -cyclopropyl		C ₂₄ H ₃₁ N ₇ O ₂ S
273002	CH ₂ NHCH ₂ - CH ₂ NHAc	trans-2-Ph- -cyclopropyl		C ₂₆ H ₃₈ N ₈ O ₃ S
273003	1-Piz-CO	trans-2-Ph- -cyclopropyl		C ₂₆ H ₃₄ N ₈ O ₃ S

SOURCE – Astra (AstraZeneca).

REFERENCES

1. Hardern, D. and Springthorpe, B. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds.* WO 9905142.

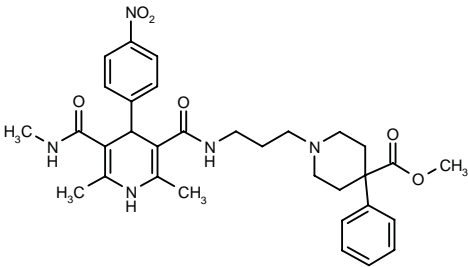
RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA
THERAPY

SNAP-5540

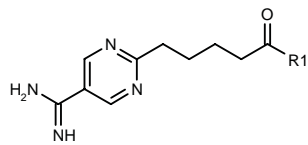
271493

(–)-1-[3-[2,6-Dimethyl-5-(methycarbamoyl)-4-(4-nitrophenyl)-1,4-dihydropyridin-3-ylcarboxamido]propyl]-4-phenylpiperidine-4-carboxylic acid methyl ester



C₃₂ H₃₉ N₅ O₆; Mol wt: 589.6891

ACTION – Platelet aggregation inhibitor proven to inhibit ADP-induced aggregation of dog platelet-rich plasma (PRP) with an IC₅₀ value of 0.11 μM. Within this series of pyrimidinylamidino β-amino acid derivatives, the following compounds are also specifically claimed:



Compound	R1	Formula
272711	-L-Asp-L-Phe-NH2	C ₂₃ H ₂₉ N ₇ O ₅
272712	NHCH(Ph)CH ₂ CO ₂ H	C ₁₉ H ₂₃ N ₅ O ₃
272713	NHCH ₂ CH ₂ CO ₂ H	C ₁₃ H ₁₉ N ₅ O ₃
272714	NHCH ₂ CH ₂ CO ₂ Et	C ₁₅ H ₂₃ N ₅ O ₃
272715	NHCH(3-Pyr)CH ₂ CO ₂ H	C ₁₈ H ₂₂ N ₆ O ₃
272716	1,3-benzodioxol-5-yl-CH(CH ₂ CO ₂ H)NH	C ₂₀ H ₂₃ N ₅ O ₅

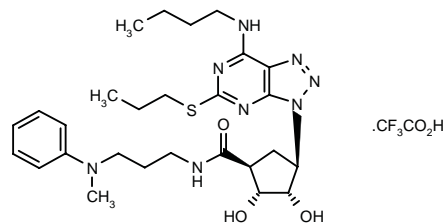
SOURCE – Monsanto.

REFERENCES

1. Bovy, P.R. et al. (Monsanto Co.) *Pyrimidinylamidino beta-amino acid derivs. useful as inhibitors of platelet aggregation.* US 5872122.

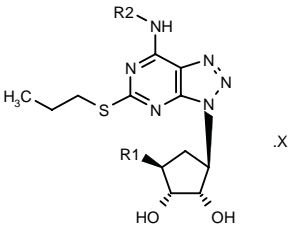
272995

(1*S*,2*R*,3*S*,4*R*)-4-[7-(Butylamino)-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxy-*N*-[3-(*N*-methyl-*N*-phenylamino)propyl]cyclopentane-1-carboxamide trifluoroacetate



C27 H40 N8 O3 S . C2 H F3 O2; Mol wt: 670.7539

ACTION – Antithrombotic agent with P2T purinoceptor-antagonist activity, claimed for the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and angina. Other specifically claimed compounds within this series of triazolo[4,5-*d*]pyrimidines include the following:



Compound	R1	R2	X	Formula
272996	CONH-(CH ₂) ₃ NH ₂	Bu	CF ₃ CO ₂ H	C ₂₀ H ₃₄ N ₈ O ₃ S .C ₂ HF ₃ O ₂
272997	trans-4-NH ₂ -cyclohexyl-NHCO	trans-2-Ph-cyclopropyl	2CF ₃ CO ₂ H	C ₂₈ H ₃₈ N ₈ O ₃ S .2C ₂ HF ₃ O ₂
272999	CH ₂ NH ₂	Bu		C ₁₇ H ₂₉ N ₇ O ₂ S
273000	NH ₂	trans-2-Ph-cyclopropyl		C ₂₁ H ₂₇ N ₇ O ₂ S
273001	(<i>E</i>)-CH=CH-CH ₂ NH ₂	trans-2-Ph-cyclopropyl		C ₂₄ H ₃₁ N ₇ O ₂ S
273002	CH ₂ NHCH ₂ -CH ₂ NHAc	trans-2-Ph-cyclopropyl		C ₂₆ H ₃₆ N ₈ O ₃ S
273003	1-Piz-CO	trans-2-Ph-cyclopropyl		C ₂₆ H ₃₄ N ₈ O ₃ S

SOURCE – Astra (AstraZeneca).

REFERENCES

1. Hardern, D. and Springthorpe, B. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds.* WO 9905142.

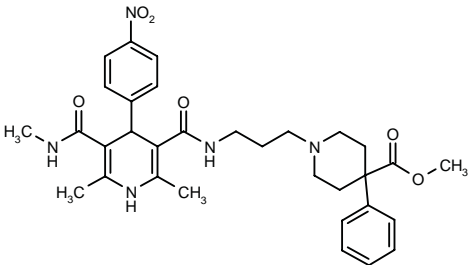
RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

SNAP-5540

271493

(–)-1-[3-[2,6-Dimethyl-5-(methycarbamoyl)-4-(4-nitrophenyl)-1,4-dihydropyridin-3-ylcarboxamido]propyl]-4-phenylpiperidine-4-carboxylic acid methyl ester



C32 H39 N5 O6; Mol wt: 589.6891

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), a potent and selective α_{1a} -adrenoceptor antagonist ($K_i = 2.42$ nM against recombinant human receptor) with > 1000-fold selectivity over α_{1b} - and α_{1d} -adrenoceptors ($K_i = 3660$ and 8710 nM, respectively) and 200-fold selectivity over other human G-protein-coupled receptors; it also showed high affinity for α_{1a} -adrenoceptors from human and dog prostatic tissue ($K_i = 3.6$ and 2.8 nM, respectively) and was devoid of activity at calcium channels. In functional studies in isolated dog prostatic tissue, it inhibited phenylephrine-induced contractions with a K_b of 1.6 nM. *In vivo* in anesthetized dogs, compound antagonized the phenylephrine-stimulated increase in intraurethral pressure ($K_b = 4.6$ μ g/kg i.v.) at doses that did not significantly influence the phenylephrine-induced increase in arterial pressure ($K_b = 74$ μ g/kg i.v.), demonstrating its selectivity for urethral α_{1a} -adrenoceptors.

SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Gluchowski, C. et al. (Synaptic Pharmaceutical Corp.) *Dihydropyridines and new uses thereof*. US 5767131, WO 9422829.

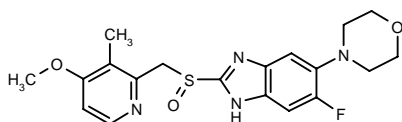
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

271897

6-Fluoro-2-(3-methyl-4-methoxy-2-pyridinyl-methylsulfinyl)-5-(4-morpholinyl)-1*H*-benzimidazole



C19 H21 F N4 O3 S; Mol wt: 404.4639

ACTION – Gastric acid antisecretory and antiulcer agent with H^+/K^+ -ATPase-inhibitory activity, reported to possess a shorter duration of action compared to known proton pump inhibitors and which is thus expected to possess an improved safety profile, i.e., a lower liability to cause gastric carcinoids. *In vitro*, compound was found to inhibit H^+/K^+ -ATPase from rabbit gastric mucosa with an IC_{50} value of 2.6 μ M (IC_{50} omeprazole = 4.35 μ M). *In vivo*, it inhibited gastric acid secretion in pylorus-ligated rats with an ED_{50} value of 3.0 ± 0.2 mg/kg i.d. (ED_{50} omeprazole = 4.96 ± 0.5 mg/kg i.d.). A representative compound from a series of benzimidazole derivatives.

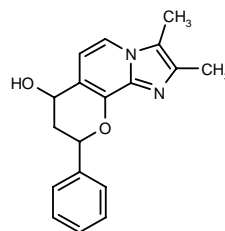
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

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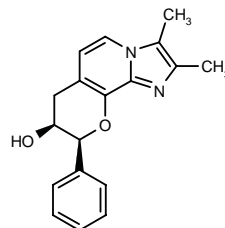
271900

2,3-Dimethyl-9-phenyl-8,9-dihydro-7*H*-imidazo[1,2-*a*]-pyrano[2,3-*c*]pyridin-7-ol



C18 H18 N2 O2; Mol wt: 294.3522

ACTION – Agent for the treatment or prevention of gastrointestinal disorders such as stomach or duodenal ulcers and gastritis, proven to produce 100% inhibition of pentagastrin-stimulated acid secretion in perfused rat stomach *in vivo* after administration of 3 μ mol/kg i.v. Another specifically claimed compound from this series of fused dihydropyrans is:



271901: C18 H18 N2 O2

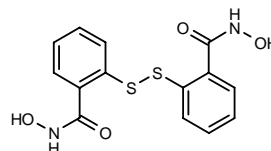
SOURCE – Byk Gulden.

REFERENCES

1. Grundler, G. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Fused dihydropyrans*. WO 9854188.

271974

2,2'-Dithiobis(benzohydroxamic acid)



C14 H12 N2 O4 S2; Mol wt: 336.3908

ACTION – Antiulcer agent with activity against *Helicobacter pylori* ($IC_{50} = 3.6$ μ M against *H. pylori* urease). Within this series of dithiodibenzohydroxamic acid derivatives, the following are also included:

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), a potent and selective α_{1a} -adrenoceptor antagonist ($K_i = 2.42$ nM against recombinant human receptor) with > 1000-fold selectivity over α_{1b} - and α_{1d} -adrenoceptors ($K_i = 3660$ and 8710 nM, respectively) and 200-fold selectivity over other human G-protein-coupled receptors; it also showed high affinity for α_{1a} -adrenoceptors from human and dog prostatic tissue ($K_i = 3.6$ and 2.8 nM, respectively) and was devoid of activity at calcium channels. In functional studies in isolated dog prostatic tissue, it inhibited phenylephrine-induced contractions with a K_b of 1.6 nM. *In vivo* in anesthetized dogs, compound antagonized the phenylephrine-stimulated increase in intraurethral pressure ($K_b = 4.6$ μ g/kg i.v.) at doses that did not significantly influence the phenylephrine-induced increase in arterial pressure ($K_b = 74$ μ g/kg i.v.), demonstrating its selectivity for urethral α_{1a} -adrenoceptors.

SOURCES – Merck & Co.; Synaptic.

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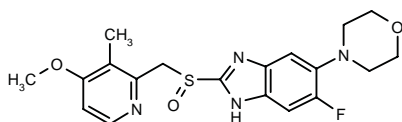
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

271897

6-Fluoro-2-(3-methyl-4-methoxy-2-pyridinyl-methylsulfinyl)-5-(4-morpholinyl)-1*H*-benzimidazole



C19 H21 F N4 O3 S; Mol wt: 404.4639

ACTION – Gastric acid antisecretory and antiulcer agent with H^+/K^+ -ATPase-inhibitory activity, reported to possess a shorter duration of action compared to known proton pump inhibitors and which is thus expected to possess an improved safety profile, i.e., a lower liability to cause gastric carcinoids. *In vitro*, compound was found to inhibit H^+/K^+ -ATPase from rabbit gastric mucosa with an IC_{50} value of 2.6 μ M (IC_{50} omeprazole = 4.35 μ M). *In vivo*, it inhibited gastric acid secretion in pylorus-ligated rats with an ED_{50} value of 3.0 ± 0.2 mg/kg i.d. (ED_{50} omeprazole = 4.96 ± 0.5 mg/kg i.d.). A representative compound from a series of benzimidazole derivatives.

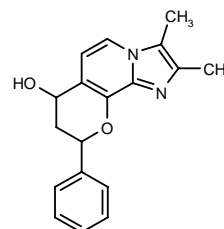
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

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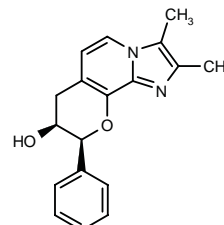
271900

2,3-Dimethyl-9-phenyl-8,9-dihydro-7*H*-imidazo[1,2-*a*]-pyrano[2,3-*c*]pyridin-7-ol



C18 H18 N2 O2; Mol wt: 294.3522

ACTION – Agent for the treatment or prevention of gastrointestinal disorders such as stomach or duodenal ulcers and gastritis, proven to produce 100% inhibition of pentagastrin-stimulated acid secretion in perfused rat stomach *in vivo* after administration of 3 μ mol/kg i.v. Another specifically claimed compound from this series of fused dihydropyrans is:



271901: C18 H18 N2 O2

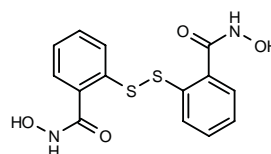
SOURCE – Byk Gulden.

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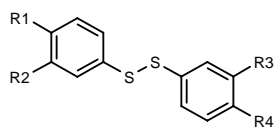
271974

2,2'-Dithiobis(benzohydroxamic acid)



C14 H12 N2 O4 S2; Mol wt: 336.3908

ACTION – Antiulcer agent with activity against *Helicobacter pylori* ($IC_{50} = 3.6$ μ M against *H. pylori* urease). Within this series of dithiodibenzohydroxamic acid derivatives, the following are also included:



Compound	R1=R4	R2=R3	Formula
271975	H	CONHOH	C ₁₄ H ₁₂ N ₂ O ₄ S ₂
271976	CONHOH	H	C ₁₄ H ₁₂ N ₂ O ₄ S ₂

SOURCE – Otsuka.

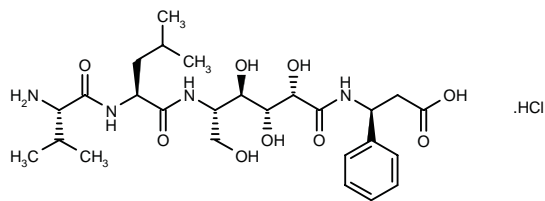
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HC-70II HCl

272593

3(S)-[2(S),3(R),4(R),6-Tetrahydroxy-5(S)-(L-valyl-L-leucylamino)hexanamido]-3-phenylpropionic acid hydrochloride



C26 H42 N4 O9 . HCl; Mol wt: 591.0977

ACTION – Agent for the treatment or prevention of gastric ulcer, duodenal ulcer, chronic gastritis and stomach cancer isolated from a culture of *Bacillus* sp. HC-70 (FERM BP-6001), with potent antibacterial activity against *Helicobacter pylori* (MIC = 0.025 µg/ml against *H. pylori* strain NTC11637). Activity was also demonstrated *in vivo* in mice infected with *H. pylori* TN2F4, where it produced complete clearance of bacterial infection at 50 mg/kg b.i.d. p.o. x 2 days.

SOURCE – Takeda.

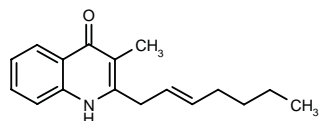
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Q-33160A

271670

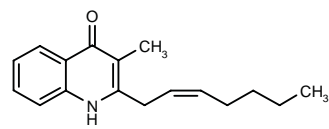
2-[2(E)-Heptenyl]-3-methyl-4(1H)-quinolinone



C17 H21 N O; Mol wt: 255.3589

ACTION – Antiulcer agent isolated from *Pseudomonas* sp. Q33160 (FERM P-16177) that acts by virtue of its selective antibacterial activity against *Helicobacter pylori* (MIC = 0.006 µg/ml); MICs against other bacteria

including aerobic and anaerobic microorganisms such as *Staphylococcus aureus* and *Escherichia coli* strains are > 50 µg/ml. Another compound from this source is:



Q-33160B [271671]: C17 H21 N O

SOURCE – Yamanouchi.

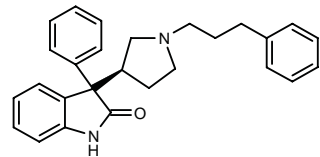
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ANTIDIARRHEAL AGENTS

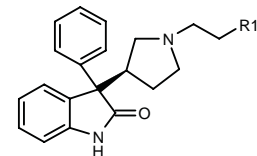
271983

3-Phenyl-3-[1-(3-phenylpropyl)pyrrolidin-3(S)-yl]indolin-2-one



C27 H28 N2 O; Mol wt: 396.5312

ACTION – Selective muscarinic M₃ receptor antagonist with pA₂ values of 8.6, 7.5 and 7.1 when tested *in vitro* for its ability to inhibit carbachol-induced contractions in M₃-bearing tissues, i.e., guinea pig ileum, urinary bladder and trachea, respectively; its affinity for M₂ receptors was much lower, as demonstrated in guinea pig left atrial preparations (pA₂ = 6.5). *In vivo*, test compound was assessed for its ability to protect against diarrhea induced by cage restraint stress in the rat (incidence: 75% in controls vs. 63% at 10 mg/kg p.o and 0-14% at 30 mg/kg p.o.). In addition, it exhibited marked activity in inhibiting oxotremorine-induced salivary secretion in the rat (ID₅₀ = 0.27 mg/kg i.v. and 8.0 mg/kg p.o.). Within this series of indole derivatives, the following are also included:



Compound	R1	Formula
271984	2,3-dihydro-5-benzofuryl	C ₂₈ H ₂₆ N ₂ O ₂
271985	OPh	C ₂₈ H ₂₆ N ₂ O ₂

SOURCE – Tokyo Tanabe.

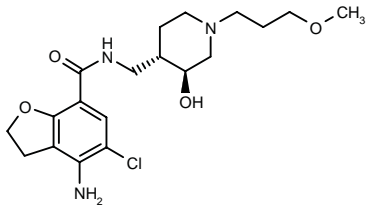
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TREATMENT OF DISORDERS OF
GASTRIC EMPTYING

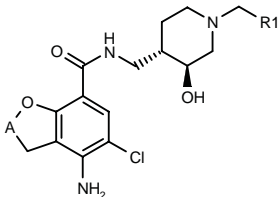
272579

trans-4-Amino-5-chloro-*N*-[3-hydroxy-1-(3-methoxypropyl)piperidin-4-ylmethyl]-2,3-dihydro-1-benzofuran-7-carboxamide



C19 H28 Cl N3 O4; Mol wt: 397.9002

ACTION – Gastrointestinal prokinetic agent proven to accelerate the emptying of an acaloric liquid meal delayed by administration of lidamide in conscious dogs at 0.0025 and 0.01 mg/kg. A representative compound from a series of bicyclic benzamides of substituted 4-(aminomethyl)piperidine derivatives, wherein the following are also included:



Compound	R1	A	Formula
272580	2-THF	-CH2-	C ₂₀ H ₂₈ ClN ₃ O ₄
272581	CH2CH2CN	-CH2-	C ₁₉ H ₂₅ ClN ₄ O ₃
272582	CH2CH2OMe	-C(Me)2-	C ₂₃ H ₃₄ ClN ₃ O ₈
272583	2-Me-1,3-dioxolan-2-yl-CH2CH2	-(CH2)2-	C ₂₃ H ₃₄ ClN ₃ O ₅

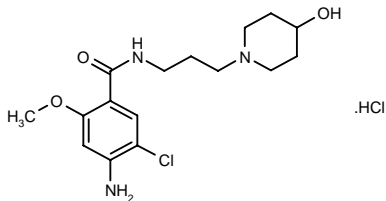
SOURCE – Janssen.

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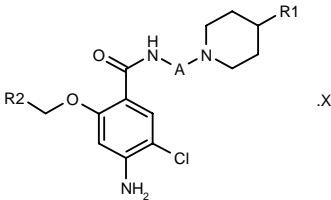
272977

4-Amino-5-chloro-*N*-[3-(4-hydroxy-1-piperidinyl)propyl]-2-methoxybenzamide hydrochloride



C16 H24 Cl N3 O3 . HCl; Mol wt: 378.2975

ACTION – Potent stimulant of both upper and lower gastrointestinal tract motility, as demonstrated *in vivo* in rabbits at 0.7 mg/kg i.v. In addition, it was shown to stimulate colon contractions in the dog at 1 mg/kg i.v., with a duration of action of > 2 h. Compound also exhibited analgesic activity in a rat model of abdominal pain following oral administration. Potentially useful for the treatment of dysfunction of the upper and lower gastrointestinal tract such as emesis, gastroesophageal reflux, dyspepsia, constipation and irritable bowel syndrome. Other compounds from this series of benzamide derivatives include the following:



Compound	R1	R2	A	X	Formula
272978	OH	H	-(CH2)2-		C ₁₅ H ₂₂ ClN ₃ O ₃
272979	OH	Me	-(CH2)3-		C ₁₇ H ₂₆ ClN ₃ O ₃
272980	CH2OH	H	-(CH2)3-		C ₁₇ H ₂₆ ClN ₃ O ₃
272981	CH2OH	H	-(CH2)2-	HCl	C ₁₆ H ₂₄ ClN ₃ O ₃ .HCl

SOURCE – Logeais.

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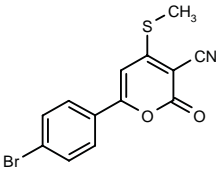
TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS

COMPOUND 91/146

272220

6-(4-Bromophenyl)-4-(methylsulfonyl)-2-oxo-2*H*-pyran-3-carbonitrile

91/146



C13 H8 Br N O2 S; Mol wt: 322.1812

ACTION – Hepatoprotective agent, a synthetic derivative of *N*-demethylricine. Given to rats at oral doses of 1, 3 and 6 mg/kg/day for 7 days, compound provided significant protection against hepatotoxicity induced by D-galactosamine and thioacetamide. In particular, it prevented rises in the activity of critical liver enzymes such as transaminases, alkaline phosphatase and glutamate dehydrogenase.

SOURCE – Central Drug Research Institute, Lucknow (IN).

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LAMIVUDINE⁺

New indication

Rec INN; BAN; USAN

184356

(–)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine

(–)-(2′*R*,5′*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

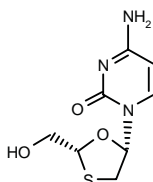
BCH-790 (former code)

GR-109714X

(–)-SddC

3TCTM

EpivirTM



C8 H11 N3 O3 S; Mol wt: 229.2589

ACTION – Antiviral agent, a reverse transcriptase inhibitor marketed for the treatment of HIV and AIDS since 1995*.

INDICATION – Oral treatment of chronic hepatitis B (HBV).

PRESENTATION – Tablets, 100 mg; oral solution, 5 mg/ml.

PROPRIETARY NAMES – *Epivir*-HBV (US); *Heptovir* (CA); *Zeffix* (HK, PH).

SOURCES – BioChem Pharma; licensed worldwide to Glaxo Wellcome except Canada, where it is marketed by a jointly owned partnership.

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52. Wolters, L.M.M. et al. *Hepatitis B viral dynamics during four weeks of lamivudine: 1500 mg versus 600 mg*. Hepatology 1998, 28(4, Part 2, Suppl.): Abst 1300.

53. *Chinese authorities approve anti-HBV drug for marketing*. DailyDrugNews.com (Daily Essentials) 1999, Jan 11.

54. *FDA committee recommends approval of Epivir-HBV*. DailyDrugNews.com (Daily Essentials) 1998, Oct 7.

55. *First approval for lamivudine in chronic hepatitis B*. DailyDrugNews.com (Daily Essentials) 1998, Aug 25.

56. *Glaxo Wellcome files for European approval of lamivudine in HBV*. DailyDrugNews.com (Daily Essentials) 1998, March 26.

57. *Health Canada approves lamivudine for treatment of chronic HBV*. DailyDrugNews.com (Daily Essentials) 1998, Dec 2.

58. *Lamivudine consistently effective as a treatment for hepatitis B*. DailyDrugNews.com (Daily Essentials) 1998, April 27.

59. *Philippines is the first market for lamivudine as an anti-HBV agent*. DailyDrugNews.com (Daily Essentials) 1998, Dec 14.

60. *Regulatory approval sought for lamivudine in U.S. for treatment of hepatitis B*. DailyDrugNews.com (Daily Essentials) 1998, June 30.

61. *The FDA approves lamivudine for the treatment of chronic HBV*. DailyDrugNews.com (Daily Essentials) 1998, Dec 10.

MONOGRAPH – Cameron, J.M. et al. Lamivudine. Drugs Fut 1993, 18(4): 319.

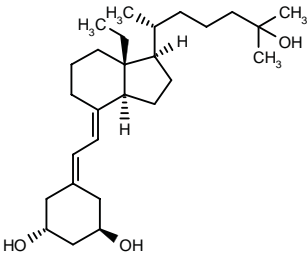
+Drug Data Rep 1996, 018(02): 0170.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

272769

1α,25-Dihydroxy-18-methyl-19-norvitamin D₃



C27 H46 O3; Mol wt: 418.6574

ACTION – Agent for the treatment of secondary hyperparathyroidism, psoriasis and cancer, a vitamin D analogue with high cell differentiation-inducing activity, as well as the ability to suppress parathyroid hormone (PTH), while having little intestinal calcium transport and bone calcium-mobilizing activity as compared to 1α,25-dihydroxyvitamin D₃. Another specifically claimed compound from this series of 18-substituted-19-nor-vitamin D derivatives is:

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33. McCaughan, G.W. et al. *Lamivudine therapy: Prophylaxis and rescue in liver transplant patients*. Transplantation 1998, 65(8, Suppl.): Abst 184.

34. Miller, D.W. and Chatterton, M.L. *An economic evaluation of lamivudine for the treatment of chronic hepatitis B infection in China*. Hepatology 1998, 28(4, Part 2, Suppl.): Abst 2437.

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51. ter Borg, F. et al. *Recovery from life-threatening, corticosteroid-unresponsive, chemotherapy-related reactivation of hepatitis B associated with lamivudine therapy*. Dig Dis Sci 1998, 43(10): 2267.

52. Wolters, L.M.M. et al. *Hepatitis B viral dynamics during four weeks of lamivudine: 1500 mg versus 600 mg*. Hepatology 1998, 28(4, Part 2, Suppl.): Abst 1300.

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61. *The FDA approves lamivudine for the treatment of chronic HBV*. DailyDrugNews.com (Daily Essentials) 1998, Dec 10.

MONOGRAPH – Cameron, J.M. et al. Lamivudine. Drugs Fut 1993, 18(4): 319.

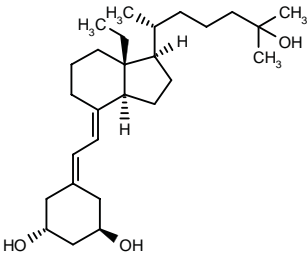
+Drug Data Rep 1996, 018(02): 0170.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

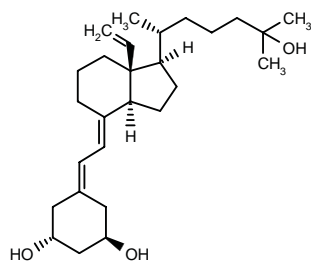
272769

1α,25-Dihydroxy-18-methyl-19-norvitamin D₃



C27 H46 O3; Mol wt: 418.6574

ACTION – Agent for the treatment of secondary hyperparathyroidism, psoriasis and cancer, a vitamin D analogue with high cell differentiation-inducing activity, as well as the ability to suppress parathyroid hormone (PTH), while having little intestinal calcium transport and bone calcium-mobilizing activity as compared to 1α,25-dihydroxyvitamin D₃. Another specifically claimed compound from this series of 18-substituted-19-nor-vitamin D derivatives is:



272770: C27 H44 O3

SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

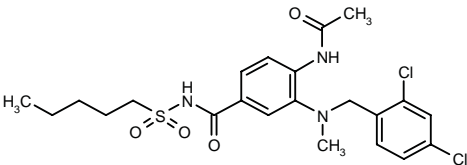
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ANTIDIABETIC DRUGS

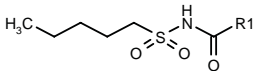
272368

4-Acetamido-3-[N-(2,4-dichlorobenzyl)-N-methylamino]-N-(pentylsulfonyl)benzamide



C22 H27 Cl2 N3 O4 S; Mol wt: 500.4443

ACTION – Agent with hypoglycemic and phosphodiesterase type 5 (PDE5)-inhibitory activity. *In vivo*, it was shown to reduce blood glucose and triglyceride levels by 60 and 104%, respectively, in *db/db* mice when given at 10 mg/kg p.o. mixed with the diet. Reported to be useful for the treatment of diabetes, hyperlipidemia, atherosclerosis, cardiovascular disorders, renal failure, stroke, autoimmune diseases, allergic rhinitis, urticaria, glaucoma, sexual impotence and pancreatitis. Other compounds from this series of aryl and heteroaryl derivatives include the following:



Compound	R1	Formula
272369	4-NH2-3-[2,4-(Cl)2-PhCH2NH]-Ph	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₃ S
272370	4-NH2-3-[2,4-(Cl)2-PhCH2N(Me)]-Ph	C ₂₀ H ₂₅ Cl ₂ N ₃ O ₃ S
272371	(E)-4-Br-2-Me-1-[2,4-(Cl)2-PhCH2]-5-imidazolyl-CH=CH	C ₁₉ H ₂₂ BrCl ₂ N ₃ O ₃ S
272372	2-Me-1-[2,4-(Cl)2-PhCH2]-5-imidazolyl-CH2CH2	C ₁₉ H ₂₅ Cl ₂ N ₃ O ₃ S
272373	(E)-2-Me-1-[2,4-(Cl)2-PhCH2]-5-imidazolyl-CH=CH	C ₁₉ H ₂₄ ClN ₃ O ₃ S

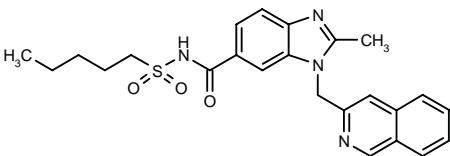
SOURCE – Fujisawa.

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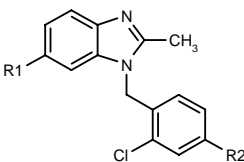
272374

1-(3-Isoquinolinylmethyl)-2-methyl-N-(pentylsulfonyl)-benzimidazole-6-carboxamide



C24 H26 N4 O3 S; Mol wt: 450.5604

ACTION – Hypoglycemic agent proven to reduce blood glucose and triglyceride levels in *db/db* mice by 44 and 77%, respectively, at 10 mg/kg p.o. twice a week x 2 weeks administered with the diet. A representative compound from a series of benzimidazole derivatives also reported to have phosphodiesterase type 5 (PDE5)-inhibitory activity and smooth muscle relaxant effects, wherein the following are also included:



Compound	R1	R2	Formula
272375	4-Me-PhSO2NHCONH	Cl	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₃ S
272376	(E)-CONHSO2CH=CHPr	Br	C ₂₁ H ₂₁ BrClN ₃ O ₃ S
272377	5-Cl-2-thienyl-SO2NHCO	Cl	C ₂₀ H ₁₄ Cl ₃ N ₃ O ₃ S ₂
272378	CONHSO2C5H11	NO2	C ₂₁ H ₂₃ ClN ₄ O ₅ S
272379	4-Me-PhSO2NHCO	CH2OPh	C ₃₀ H ₂₆ ClN ₃ O ₄ S
272380	CONHSO2C5H11	CONH-SO2C5H11	C ₂₇ H ₃₅ ClN ₄ O ₆ S ₂
272381	4-Me-PhSO2NHCO	C6H13	C ₂₉ H ₃₂ ClN ₃ O ₃ S
272382	4-vinyl-PhSO2NHCO	(E)-CH=CHPh	C ₃₂ H ₂₆ ClN ₃ O ₃ S

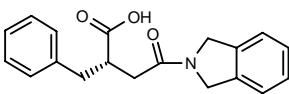
SOURCE – Fujisawa.

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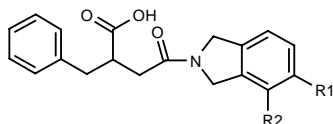
272613

2(S)-Benzyl-4-(2,3-dihydro-1H-isoindol-2-yl)-4-oxobutyric acid

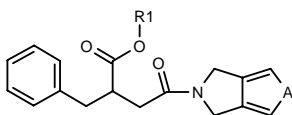


C19 H19 N O3; Mol wt: 309.3631

ACTION – Agent for the treatment of diabetes, hyperglycemia and obesity reported to reduce basal glycemia by 30-40% at a dose of 1-10 mg/kg p.o. in fasted rats. A representative compound from a series of azacycloalkane derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	Isomer	Formula
272614	H	H	R	C ₁₉ H ₁₉ NO ₃
272615	H	H		C ₁₉ H ₁₉ NO ₃
272616	F	H	S	C ₁₉ H ₁₈ FNO ₃
272617	H	F	S	C ₁₉ H ₁₈ FNO ₃



Compound	R1	A	Isomer	Formula
272618	H	O	S	C ₁₇ H ₁₇ NO ₄
272619	H	O		C ₁₇ H ₁₇ NO ₄
272620	H	S	S	C ₁₇ H ₁₇ NO ₃ S
272621	H	S	R	C ₁₇ H ₁₇ NO ₃ S
272622	H	S		C ₁₇ H ₁₇ NO ₃ S
272623	CH ₂ Ph	S	S	C ₂₄ H ₂₃ NO ₃ S

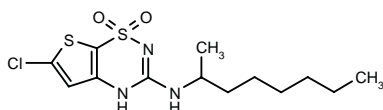
SOURCE – Synthélabo.

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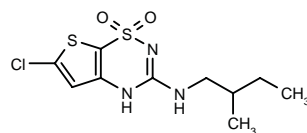
272706

6-Chloro-3-(1-methylheptylamino)-4*H*-thieno[3,2-*e*]-[1,2,4]thiadiazine-1,1-dioxide



C₁₃ H₂₀ Cl N₃ O₂ S₂; Mol wt: 349.9050

ACTION – Agent for the treatment of hyperinsulinemia and diabetes that acts by opening ATP-sensitive potassium (K_{ATP}) channels, as demonstrated *in vitro* by its ability to relax rat aorta rings contracted with phenylephrine (EC₅₀ = 2.8 μM) and to increase ⁸⁶Rb⁺ efflux from the pancreatic β-cell line RIN 5F (EC₅₀ = 5.5 μM). Another compound within this series of fused 1,2,4-thiadiazine derivatives is:



272707: C₁₀ H₁₄ Cl N₃ O₂ S₂

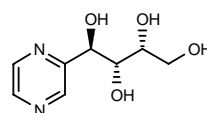
SOURCE – Novo Nordisk.

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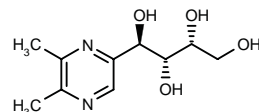
272767

(1*R*,2*R*,3*R*)-1-(2-Pyrazinyl)-1,2,3,4-butanetetraol



C₈ H₁₂ N₂ O₄; Mol wt: 200.1928

ACTION – Hypoglycemic agent reported to produce at least 10% inhibition of glycemia at a dose of 3-50 mg/kg intragastrically in mice given an oral glucose load, with very low toxicity (LD₅₀ > 2000 mg/kg p.o. in mice). Another exemplified compound from this series of 2-(1,2,3,4-tetrahydroxybutyl)pyrazine derivatives is:



272768: C₁₀ H₁₆ N₂ O₄

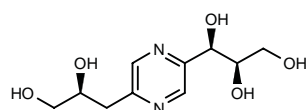
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Bashiardes, G. et al. (Rhône-Poulenc Rorer SA) *2-(1,2,3,4-Tetrahydroxybutyl)-pyrazine derivs., preparation and medicines containing them.* WO 9903838.

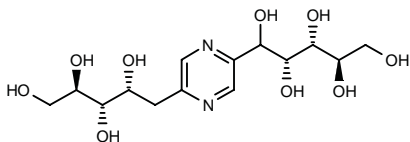
272771

(1*R*,2*R*)-1-[5-[2(*S*)-2,3-Dihydroxypropyl]-2-pyrazinyl]-1,2,3-propanetriol

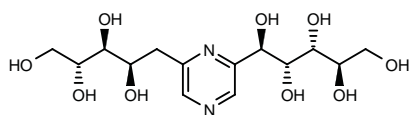


C₁₀ H₁₆ N₂ O₅; Mol wt: 244.2454

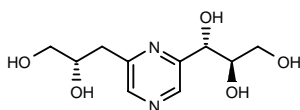
ACTION – Hypoglycemic agent, as demonstrated in mice subjected to an oral glucose load by a reduction in glycemia of at least 10% at a dose of 3-50 mg/kg intragastrically. LD₅₀ > 2000 mg/kg p.o. in mice. Claimed for use in the treatment or prevention of diabetes and complications thereof. Other exemplified compounds from this series of polyhydroxyalkylpyrazine derivatives include the following:



Compound	Isomer	Formula
272772	R	C ₁₄ H ₂₄ N ₂ O ₉
272773	S	C ₁₄ H ₂₄ N ₂ O ₉



272776: C₁₄ H₂₄ N₂ O₉



272777: C₁₀ H₁₆ N₂ O₅

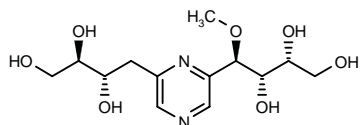
SOURCE – Rhône-Poulenc Rorer.

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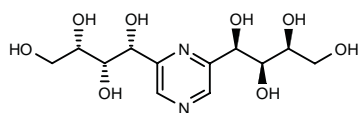
272778

(2*R*, 3*S*, 4*R*)-4-Methoxy-4-[6-[(2*S*, 3*R*)-2,3,4-trihydroxybutyl]-2-pyrazinyl]-1,2,3-butanetriol



C₁₃ H₂₂ N₂ O₇; Mol wt: 318.3238

ACTION – Hypoglycemic agent, as demonstrated in mice subjected to an oral glucose load by a reduction in glycemia of at least 10% at a dose of 3-50 mg/kg intragastrically. LD₅₀ > 2000 mg/kg p.o. in mice. Claimed for use in the treatment or prevention of diabetes and complications thereof. Another exemplified compound from this series of polyhydroxyalkylpyrazine derivatives is:



272779: C₁₂ H₂₀ N₂ O₈

SOURCE – Rhône-Poulenc Rorer.

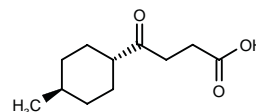
REFERENCES

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JTT-608

271571

trans-4-(4-Methylcyclohexyl)-4-oxobutanoic acid



C₁₁ H₁₈ O₃; Mol wt: 198.2602

White solid, m.p. 100.4-1.2 °C.

ACTION – Antidiabetic agent found to improve glucose tolerance in both normal and streptozotocin-diabetic rats at doses of 3-100 mg/kg and 30-100 mg/kg p.o., respectively. It did not influence fasting euglycemia in these animals up to a dose of 30 mg/kg p.o. *In vitro*, at a concentration of 200 μM it selectively enhanced glucose-induced insulin secretion in normal and diabetic rat pancreas; it appears to enhance the β-cell response to glucose in the pancreas. Currently undergoing clinical evaluation for the therapy of type II diabetes.

SOURCE – Japan Tobacco.

REFERENCES

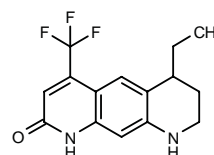
1. Shinkai, H. et al. (Japan Tobacco, Inc.) *Therapeutic agents for diabetes.* JP 97286755, WO 9730017.
2. Shinkai, H. et al. 4-(*trans*-4-Methylcyclohexyl)-4-oxobutyric acid (JTT-608). *A new class of antidiabetic agent.* J Med Chem 1998, 41(27): 5420.

TREATMENT OF MALE SEXUAL DYSFUNCTION

LG-121071

272393

6-Ethyl-4-(trifluoromethyl)-6,7,8,9-tetrahydropyrido[3,2-*g*]-quinolin-2(1*H*)-one



C₁₅ H₁₅ F₃ N₂ O; Mol wt: 296.2905

ACTION – The first orally active, nonsteroidal androgen receptor agonist with nanomolar affinity for the human receptor ($K_i = 17$ nM). In an *in vitro* functional assay, compound exhibited agonist activity ($EC_{50} = 4$ nM) in stimulating reporter gene expression (luciferase) in cotransfected CV-1 cells, with a potency and efficacy equivalent to dihydrotestosterone (DHT; $EC_{50} = 5$ nM), but no antagonist activity ($IC_{50} = 7481$ nM). Compound did not interfere with human progesterone, glucocorticoid, mineralocorticoid or estrogen receptors. When given orally at a daily dose of 20 mg/kg for 2 weeks to castrated rats, it suppressed the elevation in serum luteinizing hormone (LH) with the same efficacy as DHT (1 mg/kg/day for 2 weeks). Potentially useful as androgen replacement therapy in hypogonadal men, for the treatment of cancer cachexia and for use as a male contraceptive.

SOURCE – Ligand.

REFERENCES

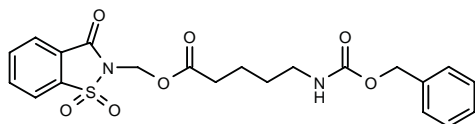
1. Edwards, J.P. et al. (Ligand Pharmaceuticals, Inc.) *Androgen receptor modulator cpds. and methods*. WO 9749709.
2. Jones, T.K. et al. (Ligand Pharmaceuticals, Inc.) *Steroid receptor modulator cpds. and methods*. EP 800519, JP 98510840, US 5688808, US 5688810, US 5693646, US 5693647, US 5696127, US 5696130, US 5696133, WO 9619458.
3. Hamann, L.G. et al. *Discovery of a potent, orally active, nonsteroidal androgen receptor agonist: 4-Ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (LG121071)*. J Med Chem 1999, 42(2): 210.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

270509

5-(Benzyloxycarbonylamino)pentanoic acid 3-oxo-2,3-dihydrobenzothiazol-2-ylmethyl ester *S,S*-dioxide



C21 H22 N2 O7 S; Mol wt: 446.4778

Oil.

ACTION – An inhibitor of human mast cell tryptase ($IC_{50} = 0.11$ μ M) with good selectivity relative to other proteases such as thrombin ($IC_{50} > 33$ μ M), trypsin ($IC_{50} > 12$ μ M), urokinase ($IC_{50} > 33$ μ M), plasmin ($IC_{50} = 33$ μ M) and factor Xa ($IC_{50} > 33$ μ M). In a mouse delayed-type hypersensitivity model of skin inflammation, compound applied to the ear (5% solution in acetone) reduced both edema (69% reduction) and myeloperoxidase content as an index of polymorphonuclear leukocyte (PMN) infiltration (96% reduction); for comparison, betamethasone dipropionate (0.1%) produced 96 and 98% inhibition, respectively. Potentially useful for the treatment of inflammatory skin diseases such as psoriasis and atopic dermatitis.

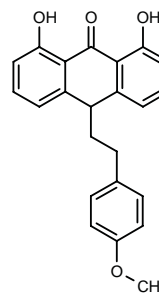
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Combrink, K.D. et al. *1,2-Benzisothiazol-3-one 1,1-dioxide inhibitors of human mast cell tryptase*. J Med Chem 1998, 41(24): 4854.

270653

1,8-Dihydroxy-10-[2-(4-methoxyphenyl)ethyl]anthracene-9(10*H*)-one



C23 H20 O4; Mol wt: 360.4070

ACTION – Inhibitor of keratinocyte growth ($IC_{50} = 0.9$ μ M in HaCaT keratinocytes) with a low potential for inducing hydroxyl radical formation and lipid peroxidation in cell membranes. Compound was at least as potent as anthralin in inhibiting keratinocyte growth, but showed significantly reduced membrane damage. Potential therapeutic agent for the treatment of hyperproliferative skin diseases such as psoriasis.

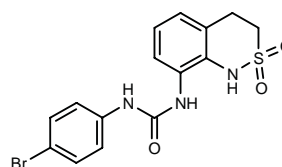
SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität, Münster (DE).

REFERENCES

1. Müller, K. and Breu, K. *10- ω -Phenylalkyl-9(10H)-anthracenones as inhibitors of keratinocyte growth with reduced membrane damaging properties*. Bioorg Med Chem Lett 1998, 8(22): 3211.

272900

N-(4-Bromophenyl)-*N'*-(3,4-dihydro-1*H*-2,1-benzothiazin-8-yl)urea *S,S*-dioxide



C15 H14 Br N3 O3 S; Mol wt: 396.2636

ACTION – CXCR1 (IL-8 α , IL-8 receptor type I) and/or CXCR2 (IL-8 β , IL-8 receptor type II) receptor antagonist with potential in the treatment of a broad range of chemokine-mediated diseases such as psoriasis, arthritis, asthma, inflammatory bowel disease, stroke, septic shock, thrombosis, graft-versus-host disease, Alzheimer's disease, restenosis and angiogenesis. It is capable of inhibiting the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to these receptors, and thereby inhibit cytokine function. Other compounds from this series of urea and thiourea derivatives include the following:

ACTION – The first orally active, nonsteroidal androgen receptor agonist with nanomolar affinity for the human receptor ($K_i = 17$ nM). In an *in vitro* functional assay, compound exhibited agonist activity ($EC_{50} = 4$ nM) in stimulating reporter gene expression (luciferase) in cotransfected CV-1 cells, with a potency and efficacy equivalent to dihydrotestosterone (DHT; $EC_{50} = 5$ nM), but no antagonist activity ($IC_{50} = 7481$ nM). Compound did not interfere with human progesterone, glucocorticoid, mineralocorticoid or estrogen receptors. When given orally at a daily dose of 20 mg/kg for 2 weeks to castrated rats, it suppressed the elevation in serum luteinizing hormone (LH) with the same efficacy as DHT (1 mg/kg/day for 2 weeks). Potentially useful as androgen replacement therapy in hypogonadal men, for the treatment of cancer cachexia and for use as a male contraceptive.

SOURCE – Ligand.

REFERENCES

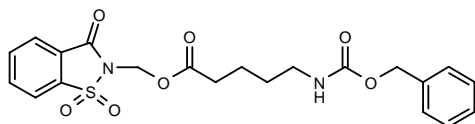
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

270509

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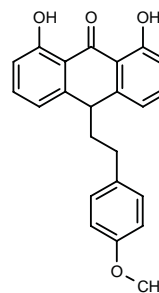
SOURCE – Bristol-Myers Squibb.

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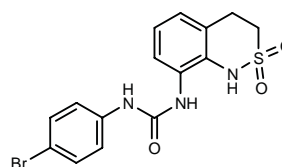
SOURCES – Universität Regensburg, Regensburg (DE); Westfälische Wilhelms-Universität, Münster (DE).

REFERENCES

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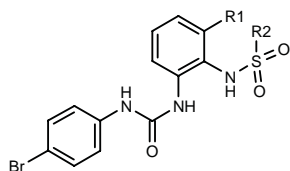
272900

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C15 H14 Br N3 O3 S; Mol wt: 396.2636

ACTION – CXCR1 (IL-8 α , IL-8 receptor type I) and/or CXCR2 (IL-8 β , IL-8 receptor type II) receptor antagonist with potential in the treatment of a broad range of chemokine-mediated diseases such as psoriasis, arthritis, asthma, inflammatory bowel disease, stroke, septic shock, thrombosis, graft-versus-host disease, Alzheimer's disease, restenosis and angiogenesis. It is capable of inhibiting the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78, particularly IL-8, to these receptors, and thereby inhibit cytokine function. Other compounds from this series of urea and thiourea derivatives include the following:



Compound	R1,R2	Formula
272901	-CH=CH-	C ₁₅ H ₁₂ BrN ₃ O ₃ S
272902	-COCH ₂ -	C ₁₅ H ₁₂ BrN ₃ O ₄ S

SOURCE – SmithKline Beecham.

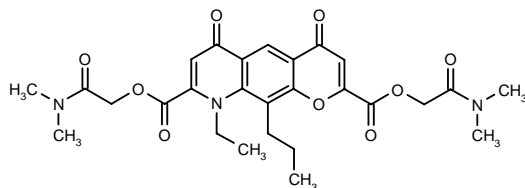
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1. Nie, H. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9834929.

MISCELLANEOUS DERMATOLOGIC DRUGS

271645

9-Ethyl-4,6-dioxo-10-propyl-6,9-dihydro-4*H*-pyrano-[3,2-*g*]quinoline-2,8-dicarboxylic acid bis[2-(dimethyl-amino)-2-oxoethyl] ester



C27 H31 N3 O9; Mol wt: 541.5539

ACTION – Topical antiallergic and antiinflammatory agent with significant inhibitory effects on the immediate allergic reaction in sensitized rats (PCA reaction), as well as on the delayed-type reaction in mouse ear.

SOURCE – Ikeda Mohando.

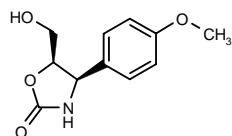
REFERENCES

1. Sasaki, Y. (Ikeda Mohando) *Pyranquinoline derivs., their preparation method and their dermal agents for the treatment of allergic disease*. JP 98279582.

CYTOXAZONE

271167

(4*R*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one



C11 H13 N O4; Mol wt: 223.2267

Colorless crystals, *m.p.* 118-21 °C, $[\alpha]_D^{23}$ -71° (*c* 0.1 MeOH).

ACTION – Cytokine modulator produced by *Streptomyces* sp. RK95-31 (FERM P-16171) isolated from a soil sample. In whole spleen from mice, compound at concentrations of 6.25-25 µg/ml significantly inhibited IL-4 and IL-10 production induced by pokeweed mitogen. Compound inhibited the production of IL-4 and IL-10 from cloned Th2 cells, but was inactive against granulocyte-macrophage colony-stimulating factor (GM-CSF) production from cloned Th1 cells, indicating that the inhibition of cytokine production is mediated by the signaling pathway of Th2 cells. Potentially useful as an immunosuppressant for disorders associated with expansion of allergen-specific Th2 cells such as atopic dermatitis.

SOURCE – Institute of Physical and Chemical Research, Saitama (JP).

REFERENCES

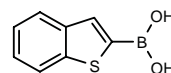
1. Kakeya, H. et al. *Cytoxazone: A novel cytokine modulator containing a 2-oxazolidinone ring produced by Streptomyces sp.* J Org Chem 1999, 64(3): 1052.
2. Kakeya, H. et al. *Isolation and biological activity of a novel cytokine modulator, cytoxazone*. J Antibiot 1998, 51(12): 1126.

ANTIINFECTIVE THERAPY

AINTIBIOTICS

270362

Benzo[*b*]thiophene-2-boronic acid



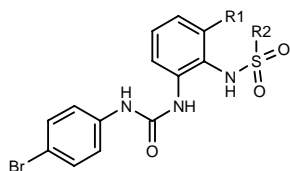
C8 H7 B O2 S; Mol wt: 178.0183

ACTION – Boronic acid-based non-β-lactam inhibitor of class C β-lactamases (*K_i* = 27 nM, *IC*₅₀ = 150 nM against *Escherichia coli* AmpC) with high specificity over β-trypsin and elastase (*IC*₅₀ = 200 µM or more) and little activity against α-chymotrypsin (*IC*₅₀ = 5 µM). Compound potentiated the activity of β-lactam antibiotics such as amoxicillin and ceftazidime against bacteria expressing class C β-lactamases.

SOURCE – Northwestern University (US).

REFERENCES

1. Weston, G.S. and Shoichet, B.K. (Northwestern University) *Inhibitors of beta-lactamases and uses therefor*. WO 9856392.
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Compound	R1,R2	Formula
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SOURCE – SmithKline Beecham.

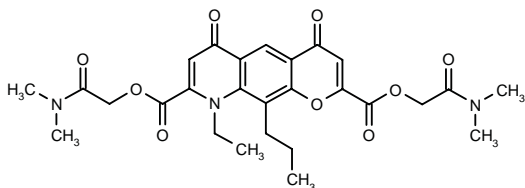
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MISCELLANEOUS DERMATOLOGIC DRUGS

271645

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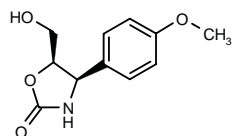
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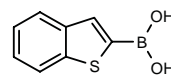
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ANTIINFECTIVE THERAPY

AINTIBIOTICS

270362

Benzo[*b*]thiophene-2-boronic acid



C8 H7 B O2 S; Mol wt: 178.0183

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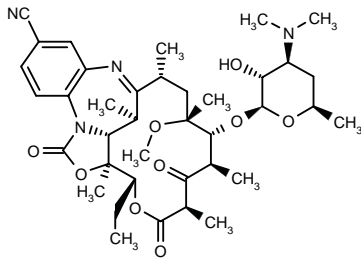
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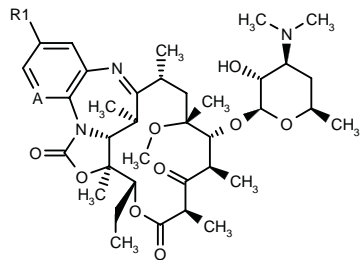
271905

[4*S*-(4 α ,5 β ,8 β ,10 β ,11 α ,12 β ,14 α ,21 β ,22 β)]-18-Cyano-5-ethyl-12-methoxy-4,8,10,12,14,21-hexamethyl-11-[3,4,6-trideoxy-3-(dimethylamino)- β -D-glucopyranosyloxy]-4,5,7,8,9,10,11,12,13,14-decahydro-2*H*-15,1,4-ethanylidene-3,6,1,16-dioxadiazacyclooctadecine-2,7,9-trione



C38 H54 N4 O9; Mol wt: 710.8636

ACTION – Semisynthetic macrolide antibiotic with an improved profile of activity compared to erythromycin. It was active *in vitro* against Gram-positive bacteria including *Staphylococcus aureus* ATCC 6538P (MIC = 0.39 μ g/ml) and *Streptococcus pyogenes* EE61 (MIC = 0.01 μ g/ml). Within this series of multicyclic erythromycin derivatives, the following are also included:



Compound	R1	A	Formula
271906	H	CH	C ₃₇ H ₅₅ N ₃ O ₉
271907	Me	CH	C ₃₈ H ₅₇ N ₃ O ₉
271908	OMe	CH	C ₃₈ H ₅₇ N ₃ O ₁₀
271909	H	N	C ₃₆ H ₅₄ N ₄ O ₉

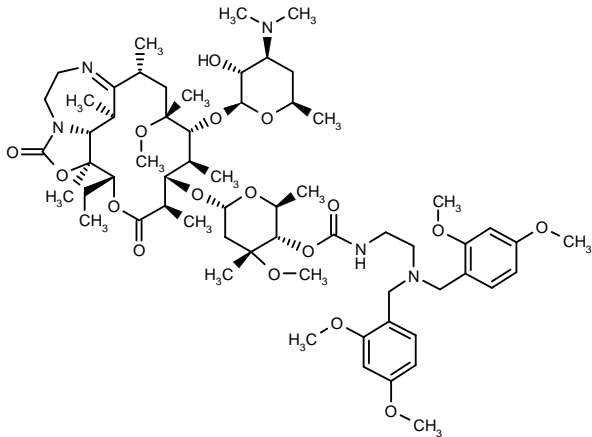
SOURCE – Abbott.

REFERENCES

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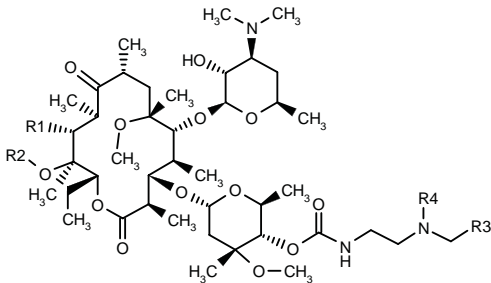
272759

11-Amino-4''-O-[*N*-[2-[*N,N*-bis(2,4-dimethoxybenzyl)amino]ethyl]carbamoyl]-9-deoxy-11-deoxy-*N*⁹,*N*¹¹-ethylene-9-imino-6-O-methylerythromycin A *N*¹¹,*O*¹²-cyclic carbamate

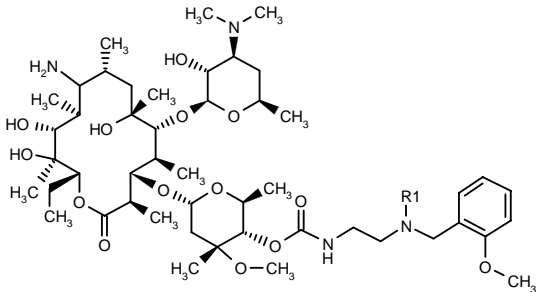


C62 H97 N5 O17; Mol wt: 1184.4660

ACTION – Macrolide antibiotic for the treatment of bacterial and protozoal infections, also reported to be useful for the treatment of cancer, particularly non-small cell lung cancer. Within this series of C-4'' substituted macrolides, the following are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
272760	-NHCO-		3-furyl	H	C ₄₇ H ₇₈ N ₄ O ₁₅
272764	OH	H	CH ₂ CH(Me)-OMe	3-Et-5-Me-4-oxazolyl	C ₅₃ H ₉₄ N ₄ O ₁₆
272765	OH	H	H	3,5-(Me)2-4-isoxazolyl-CH ₂	C ₄₈ H ₈₄ N ₄ O ₁₅
272766	-NHCO-		2-MeO-5-i-Pr-Ph	H	C ₅₃ H ₈₈ N ₄ O ₁₅



Compound	R1	Formula
272761	i-PrOCH ₂	C ₅₃ H ₉₄ N ₄ O ₁₅
272763	Et	C ₅₁ H ₉₀ N ₄ O ₁₄

SOURCE – Pfizer.

REFERENCES

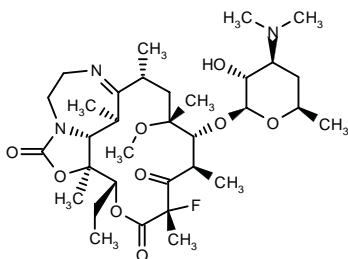
1. Brighty, K.E. et al. (Pfizer Products Inc.) *C-4'' Substd. macrolide antibiotics*. EP 895999.

A-241550

268262

11-Amino-9-deoxo-11-deoxy-3-des(cladinosyloxy)-2-fluoro-9-*N*,11-*N*-ethylene-9-imino-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate

2F-TE-802



C33 H54 F N3 O9; Mol wt: 655.7996

ACTION – Macrolide antibiotic derived from the tricyclic ketolide TE-802⁺, with improved *in vitro* potency against resistant strains particularly *Haemophilus influenzae*. It gave MIC values of 0.1 µg/ml against *Staphylococcus aureus* strains susceptible to erythromycin or with inducible MLS resistance, of 0.03 µg/ml against erythromycin-susceptible *Staphylococcus pyogenes* and *Streptococcus pneumoniae*, of 0.5 µg/ml against strains of the latter two bacteria with erythromycin resistance due to an efflux mechanism, and of 2 µg/ml against *H. influenzae*. In mouse *S. aureus*, *S. pneumoniae* and *H. influenzae* infection models, compound displayed improved efficacy versus other macrolides, giving ED₅₀ values of 9.4, 7.2 and 35.9 mg/kg, respectively (ED₅₀ TE-802 = 13, 10 and > 60 mg/kg, respectively).

SOURCE – Abbott.

REFERENCES

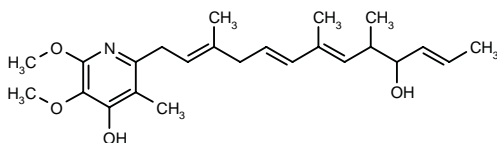
1. Phan, L.T. et al. *2-Substituted tricyclic ketolides: New antibacterial macrolides. - Synthesis and biological activity*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-127.

*Drug Data Rep 1995, 017(010): 0928.

CRPF-2721-6

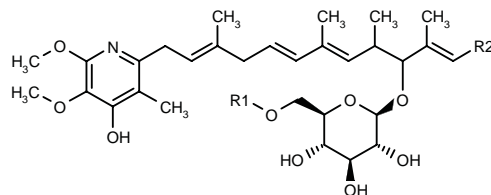
271987

2-[10-hydroxy-3,7,9-trimethyl-2(*E*),5(*E*),7(*E*),11(*E*)-tridecatetraenyl]-5,6-dimethoxy-3-methylpyridin-4-ol



C24 H35 N O4; Mol wt: 401.5435

ACTION – Antibiotic isolated from *Streptomyces* sp. CRPF-2721 (FERM BP-5918), showing some activity against several microorganisms such as *Bacillus subtilis* (MIC = 41.7 µg/ml) and *Staphylococcus aureus* ATCC 6538P (MIC = 83.3 µg/ml). Other compounds from this source are:



Compound	R1	R2	Formula
CRPF-2721-3 [271988]	Ac	Me	C ₃₃ H ₄₉ NO ₁₀
CRPF-2721-5 [271989]	H	Et	C ₃₂ H ₄₉ NO ₉

SOURCE – Kyowa Hakko.

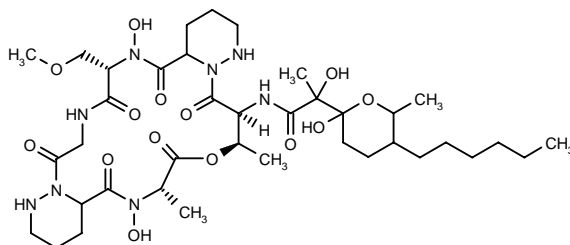
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1. Takashima, A. et al. (Kyowa Hakko Kogyo Co., Ltd.) *CRPF-2721 cpds*. JP 98330363.

DIPERAMYCIN

271159

N-[6,18-Dihydroxy-7(*S*)-(methoxymethyl)-19(*S*),21(*R*)-dimethyl-5,8,11,17,20,24-hexaoxoperhydrodipyrizino[6,1-*f*:6',1'-*o*][1,4,7,10,13,16]oxapentaazacyclononadecin-23(*S*)-yl]-2-(5-hexyl-2-hydroxy-6-methyl-tetrahydropyran-2-yl)-2-hydroxypropionamide



C38 H64 N8 O14; Mol wt: 856.9656

White powder, m.p. 152-4 °C (decomp.), [α]_D²⁰ +25.7°.

ACTION – Antibiotic obtained from the fermentation broth of *Streptomyces griseoaurantiacus* MK393-AF2, with potent activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MIC = 0.1-0.20 µg/ml) and *Bacillus* spp. (MIC = 0.10-0.39 µg/ml); it was inactive against Gram-negative bacteria and showed moderate activity against *Mycobacterium smegmatis* and *Candida albicans* (MIC = 12.5 µg/ml). Diperamycin exhibited strong growth-inhibitory effects against various tumor cell lines, with IC₅₀ values of 0.009-0.098 µg/ml. In mice, compound was lethal at a dose of 9.4 mg/kg i.v.

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

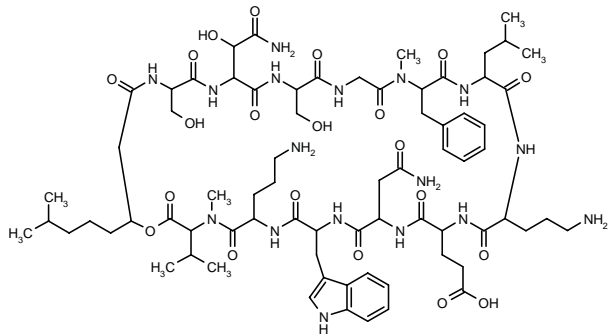
1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Novel antibiotic, diperamycin, and its preparation method*. JP 98287681.

2. Matsumoto, N. et al. *Diperamycin, a new antimicrobial antibiotic produced by Streptomyces griseoaurantiacus MK393-AF2. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities*. J Antibiot 1998, 51(12): 1087.

WAP-8294A2¹⁻³

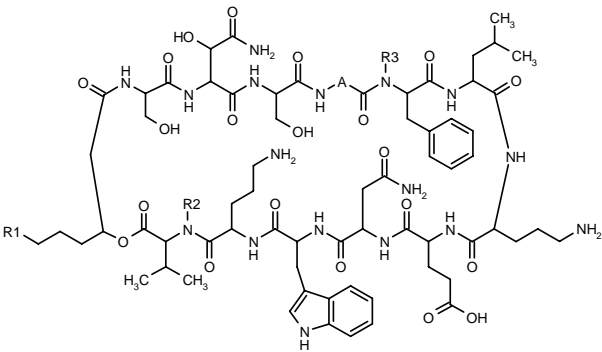
269613

6,18-Bis(3-aminopropyl)-24-benzyl-33-(1-carbamoyl-1-hydroxymethyl)-12-(carbamoylmethyl)-15-(2-carboxyethyl)-30,36-bis(hydroxymethyl)-9-(1*H*-indol-3-ylmethyl)-21-isobutyl-3-isopropyl-4,25-dimethyl-40-(4-methylpentyl)-1-oxa-4,7,10,13,16,19,22,25,28,31,34,37-dodecaazacyclotetracontane-2,5,8,11,14,17,20,23,26,29,32,35,38-tridecaone



C73 H111 N17 O21; Mol wt: 1562.7780

ACTION – Antibiotic produced by *Lysobacter* sp.WAP-8294, with strong activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 0.78 µg/ml) and vancomycin-resistant enterococci (VRE; MIC = 6.25 µg/ml); its activity against MRSA was significantly enhanced by addition of 10% human serum (MIC = 0.1 µg/ml). Compound was inactive against Gram-negative bacteria, fungi and yeasts and showed weak cytotoxicity against mouse leukemia L1210 cells (IC₅₀ = 34 µg/ml). It appears to act by damaging membranes in the target cells, interacting selectively with membrane phospholipids. *In vivo*, WAP-8294A2 was 14 times more active than vancomycin in systemic MRSA-infected mice (ED₅₀ = 0.38 and 5.3 mg/kg s.c., respectively). In mice, compound was not toxic at up 200 mg/kg p.o., 100 mg/kg i.p. and 50 mg/kg i.v. Other compounds produced by the same organism are:



Compound	R1	R2	R3	A	Formula
WAP-8294A1 [269614] ^{1,2}	Et	Me	Me	-CH2-	C ₇₂ H ₁₀₉ N ₁₇ O ₂₁
WAP-8294A4 [269615] ^{1,2}	i-Bu	Me	Me	-CH2-	C ₇₄ H ₁₁₃ N ₁₇ O ₂₁
WAP-8294Ax8 [269616] ^{1,2}	i-Pr	H	Me	-CH2-	C ₇₂ H ₁₀₉ N ₁₇ O ₂₁
WAP-8294Ax9 [269617] ^{1,2}	i-Pr	Me	H	-CH2-	C ₇₂ H ₁₀₉ N ₁₇ O ₂₁
WAP-8294Ax13 [269618] ^{1,2}	i-Pr	Me	Me	-(CH2)2-	C ₇₄ H ₁₁₃ N ₁₇ O ₂₁

SOURCE – Wakamoto.

REFERENCES

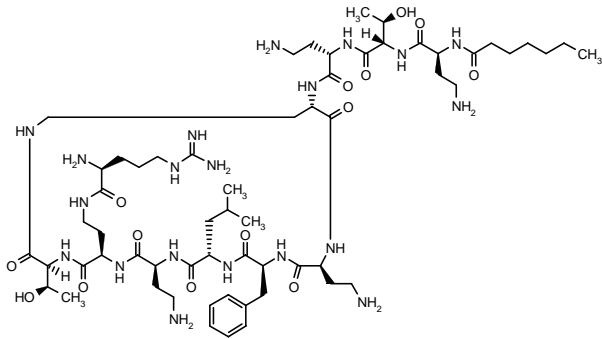
1. Nakaya, S. et al. (Wakamoto Pharmaceutical Co., Ltd.) *Antibiotic WAP-8294A, method for preparing the same and antibacterial compsn*. EP 668358.

2. Kato, A. et al. *A new anti-MRSA antibiotic complex, WAP-8294A. I. Taxonomy, isolation and biological activities*. J Antibiot 1998, 51(10): 929.

3. Kato, A. et al. *WAP-8294A2, a novel anti-MRSA antibiotic produced by Lysobacter sp..* J Am Chem Soc 1997, 119(28): 6680.

270695

(3*S*,6*R*,9*S*,12*S*,15*R*,18*S*,21*S*)-21-[4-Amino-2(*S*)-[*N*^α-[4-amino-2(*S*)-heptanamido]butyramido]-L-threonyl-amino]butyramido]-9,18-bis(2-aminoethyl)-6-[2-(L-arginyl-amino)ethyl]-3-[1(*R*)-hydroxyethyl]-12-isobutyl-1,4,7,10,13,16,19-heptaazacyclotricosane-2,5,8,11,14,17,20-heptaone



C60 H106 N20 O14; Mol wt: 1331.6230

ACTION – Antibacterial agent, polymyxin B derivative active against Gram-positive and Gram-negative bacteria such as *Pseudomonas*, *Escherichia coli* and *Staphylococcus*, with geometric mean MIC values of 0.030, 0.160 and 2.0 μM , respectively; the *in vitro* antibacterial activity of the compound was comparable to that of polymyxin B. *In vivo*, compound protected mice from *Pseudomonas aeruginosa* infection with an ED_{50} of 0.25 mg/kg s.c. and it showed low toxicity after i.v. administration (LD_{50} = 15 mg/kg), with a significantly improved therapeutic index ($\text{LD}_{50}/\text{ED}_{50}$ = 60) compared to polymyxin B.

SOURCE – Schering-Plough.

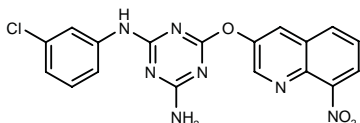
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1. Weinstein, J. et al. *Selective chemical modifications of polymyxin B*. Bioorg Med Chem Lett 1998, 8(23): 3391.

ANTIBACTERIAL DRUGS

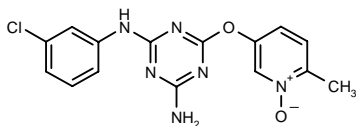
272213

4-(3-Chlorophenylamino)-6-(8-nitro-3-quinolinyloxy)-1,3,5-triazin-2-amine



C18 H12 Cl N7 O3; Mol wt: 409.7918

ACTION – Antibacterial agent that acts by inhibiting DNA gyrase, in particular from Gram-positive bacteria. *In vitro*, compound was active against novobiocin-resistant *Staphylococcus aureus* (MIC = 2.0 $\mu\text{g}/\text{ml}$), methicillin/quinolone-resistant *S. aureus* (MIC = 2.0 $\mu\text{g}/\text{ml}$), methicillin-resistant coagulase-negative staphylococci (MIC = 2.0 $\mu\text{g}/\text{ml}$), *Streptococcus pyogenes* C203 (MIC = 4.0 $\mu\text{g}/\text{ml}$), *Enterococcus faecalis* (MIC = 4.0 $\mu\text{g}/\text{ml}$) and *Bacillus subtilis* (MIC = 4.0 $\mu\text{g}/\text{ml}$). Another compound from this series of triazine derivatives is:



272214: C15 H13 Cl N6 O2

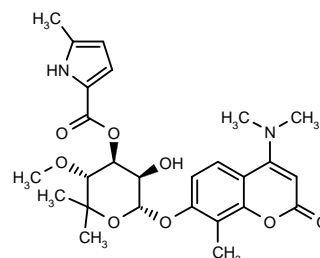
SOURCE – Zeneca (AstraZeneca).

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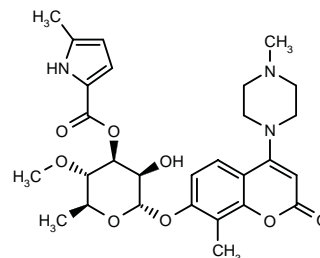
272294

7-[6-Deoxy-4-O,5-C-dimethyl-3-O-(5-methyl-1H-pyrrol-2-ylcarbonyl)- α -L-mannopyranosyl]-4-(dimethylamino)-8-methyl-2H-1-benzopyran-2-one



C26 H32 N2 O8; Mol wt: 500.5448

ACTION – Antibacterial agent active against Gram-positive bacteria including strains of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes*, that acts by inhibiting DNA gyrase B (IC_{50} < 5 $\mu\text{g}/\text{ml}$). Another specifically claimed compound from this series of ribose-substituted chromene derivatives is:



272295: C28 H35 N3 O8

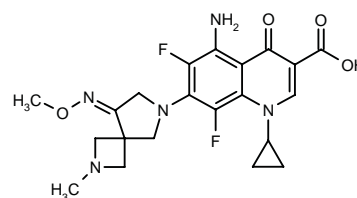
SOURCE – Hoechst Marion Roussel.

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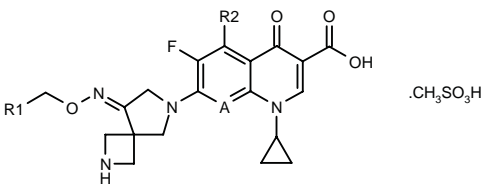
272316

5-Amino-1-cyclopropyl-6,8-difluoro-7-[2-methyl-8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21 H23 F2 N5 O4; Mol wt: 447.4397

ACTION – Quinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* 503 (MIC = 0.004 $\mu\text{g}/\text{ml}$ vs. 0.391 $\mu\text{g}/\text{ml}$ for ciprofloxacin) and *Escherichia coli* TEM (MIC = 0.013 $\mu\text{g}/\text{ml}$ vs. 0.007 $\mu\text{g}/\text{ml}$ for ciprofloxacin). LD_{50} > 320 mg/kg i.v. in mice. Within this series of quinolinecarboxylic acid derivatives, the following are also included:



Compound	R1	R2	A	Formula
272317	H	H	N	C ₁₉ H ₂₀ FN ₅ O ₄ .CH ₄ O ₃ S
272318	H	NH ₂	C(F)	C ₂₀ H ₂₁ F ₂ N ₅ O ₄ .CH ₄ O ₃ S
272319	Me	NH ₂	C(F)	C ₂₁ H ₂₃ F ₂ N ₅ O ₄ .CH ₄ O ₃ S

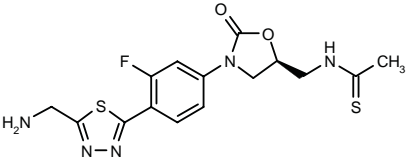
SOURCE – Dong-Wha.

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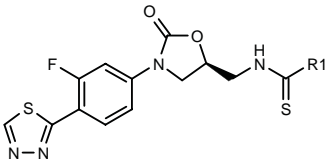
272540

N-[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



C15 H16 F N5 O2 S2; Mol wt: 381.4544

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* UC 9213 (MIC < 0.5 µg/ml), *Streptococcus pneumoniae* UC 9912 (MIC < 0.5 µg/ml) and *Haemophilus influenzae* HI30063 (MIC < 0.5 µg/ml). Compound is also reported to be active against anaerobic organisms such as *Bacteroides* spp., and acid-fast organisms such as *Mycobacterium tuberculosis*. Other compounds within this series of thiadiazolyl- and oxadiazolyl-phenyloxazolidinones include the following:



Compound	R1	Formula
272541	Me	C ₁₄ H ₁₃ FN ₄ O ₂ S ₂
272542	NH ₂	C ₁₃ H ₁₂ FN ₅ O ₂ S ₂
272543	Et	C ₁₅ H ₁₅ FN ₄ O ₂ S ₂

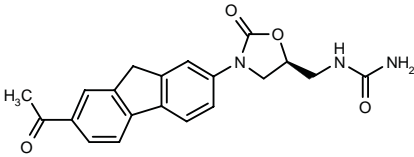
SOURCE – Pharmacia & Upjohn.

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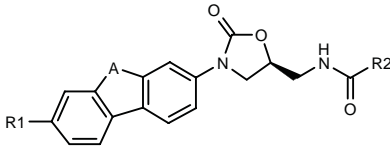
272717

N-[3-(7-Acetyl-9H-fluoren-2-yl)-2-oxooxazolidin-5(S)-ylmethyl]urea



C20 H19 N3 O4; Mol wt: 365.3871

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria such as *Staphylococcus aureus* strains 133 and 9TV (MIC = 0.25 and 0.25 µg/ml, respectively), as well as mycobacteria such as *Mycobacterium smegmatis* DSM 43061 and 43465 (MIC = 1 and 0.25 µg/ml, respectively), *Haemophilus influenzae* and anaerobes. Other compounds from this series of tricyclic substituted oxazolidinones include the following:



Compound	R1	R2	A	Formula
272718	H	CH ₂ Cl	CH ₂	C ₁₉ H ₁₇ ClN ₂ O ₃
272719	H	H	CH ₂	C ₁₈ H ₁₆ N ₂ O ₃
272720	Ac	Me	CH ₂	C ₂₁ H ₂₀ N ₂ O ₄
272721	H	Me	O	C ₁₈ H ₁₆ N ₂ O ₄
272722	H	NH ₂	O	C ₁₇ H ₁₅ N ₃ O ₄

SOURCE – Bayer.

REFERENCES

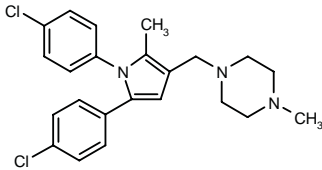
1. Bartel, S. et al. (Bayer AG) *Tricyclically substd. oxazolidinones.* WO 9903846.

ANTIMYCOBACTERIAL AGENTS

BM-212

272329

1-[1,5-Bis(4-chlorophenyl)-2-methyl-1H-pyrrol-3-yl-methyl]-4-methylpiperazine



C23 H25 Cl2 N3; Mol wt: 414.3775

ACTION – Antibacterial agent, a pyrrole derivative proven to have strong activity against *Mycobacterium tuberculosis* (MIC = 0.7-1.5 µg/ml), as well as against other mycobacterial strains such as *Mycobacterium avium* (MIC = 0.4-3.1 µg/ml), *Mycobacterium kansasii* (MIC = 3.1-6.2 µg/ml), *Mycobacterium fortuitum* (MIC = 3.1-12.5 µg/ml) and *Mycobacterium smegmatis* (MIC = 3.1-25 µg/ml). Compound was also active against some strains resistant to ethambutol, amikacin, streptomycin, rifampin and rifampicin. In human U937 cells, compound showed bactericidal activity against intracellular mycobacteria (MIC = 0.5 µg/ml) but did not inhibit cellular replication at up to 12.5 µg/ml. BM-212 was also active against several species of yeasts including *Candida albicans* and *Cryptococcus neoformans*.

SOURCE – Università degli Studi di Roma "La Sapienza", Roma (IT).

REFERENCES

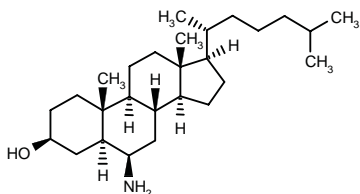
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ANTIFUNGAL AGENTS

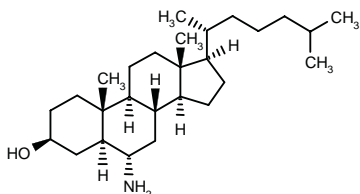
271211

6β-Amino-5α-cholestan-3β-ol



C27 H49 N O; Mol wt: 403.6901

ACTION – Potentially lymphotropic antifungal agent, an ergosterol biosynthesis inhibitor with antifungal activity against *Saccharomyces cerevisiae* (IC₅₀ < 15 µM) and *Candida albicans* (IC₅₀ < 31 µM). A candidate for the therapy of systemic and deeply invasive fungal infections. Another aminocholestanol compound is:



271210: C27 H49 NO

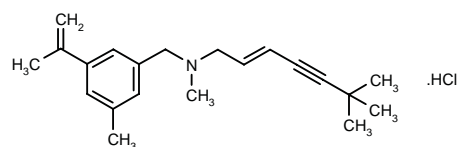
SOURCE – Université de La Rochelle, La Rochelle (FR).

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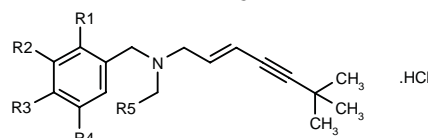
272116

N-[6,6-Dimethyl-2(*E*)-hepten-4-ynyl]-*N*-methyl-*N*-(3-methyl-5-isopropenylbenzyl)amine hydrochloride

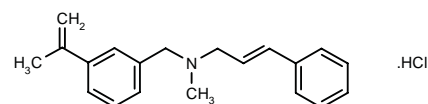


C21 H29 N . HCl; Mol wt: 331.9280

ACTION – Antifungal agent with potent *in vitro* activity against dermatophytes such as *Trichophyton mentagrophytes* IFO 5811 (MIC = 0.1 µg/ml) and *Microsporum gypseum* IFO 8231 (MIC = 0.2 µg/ml). Within this series of amine derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
272118	H	C(Me)=CH2	H	H	H	C ₂₀ H ₂₇ N.HCl
272119	H	vinyl	H	H	H	C ₁₉ H ₂₅ N.HCl
272131	H	CH=C(Me)2	H	H	H	C ₂₁ H ₂₉ N.HCl
272132	H	C(Et)=CH2	H	H	H	C ₂₁ H ₂₉ N.HCl
272134	H	(Z)-C(Me)=CHMe	H	H	H	C ₂₁ H ₂₉ N.HCl
272136	C(Me)=CH2	H	H	H	H	C ₂₀ H ₂₇ N.HCl
272137	H	C(Me)=CH2	H	H	Me	C ₂₁ H ₂₉ N.HCl
272139	Me	C(Me)=CH2	H	H	H	C ₂₁ H ₂₉ N.HCl
272140	H	C(Me)=CH2	H	F	H	C ₂₀ H ₂₆ FN.HCl
272141	H	C(Me)=CH2	Me	H	H	C ₂₁ H ₂₉ N.HCl



272138: C20 H23 N . HCl

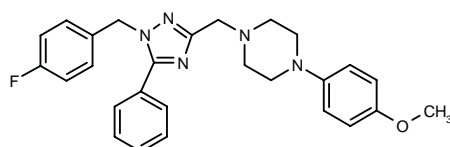
SOURCE – Pola Chemical.

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272332

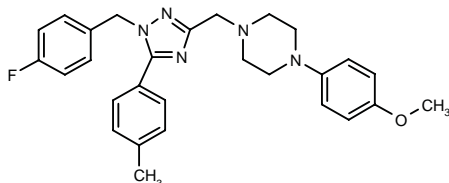
1-[1-(4-Fluorobenzyl)-5-phenyl-1*H*-1,2,4-triazol-3-yl-methyl]-4-(4-methoxyphenyl)piperazine



C27 H28 F N5 O; Mol wt: 457.5502

M.p. 124-5 °C.

ACTION – Antifungal agent active against a variety of fungi including *Aspergillus niger* (MIC = 195 µg/ml), *Aspergillus versicolor* (MIC = 212 µg/ml) and *Cladosporium cladosporioides* (MIC = 45 µg/ml). Compound was also active against *Streptococcus faecalis* (MIC = 165 µg/ml) but showed weak antibacterial activity against *Staphylococcus aureus* (MIC > 250 µg/ml) and no activity against *Bacillus subtilis*, *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Another related 3-piperazinylmethyl-5-aryl-1*H*-1,2,4-triazole is:



272333: C₂₈ H₃₀ F N₅ O

SOURCE – University of Athens, Athens (GR).

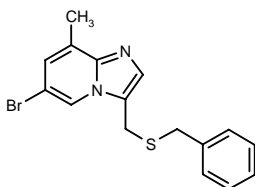
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1. Papakonstantinou-Garoufalias, S.S. et al. *Synthesis, antifungal activity and antibacterial evaluation of some 3-piperazinylmethyl-5-aryl-1*H*-1,2,4-triazoles*. *Arzneim-Forsch Drug Res* 1998, 48(10): 1019.

ANTIVIRAL DRUGS

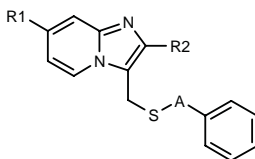
270829

3-(Benzylsulfanylmethyl)-6-bromo-8-methylimidazo[1,2-*a*]pyridine



C₁₆ H₁₅ Br N₂ S; Mol wt: 347.2785

ACTION – Antiviral agent with excellent activity against human cytomegalovirus (HCMV; IC₅₀ = 0.12 µg/ml) and low cytotoxicity (IC₅₀ > 50 µg/ml in HEL cells), giving a therapeutic index of > 417. Compound was also able to inhibit the cytopathogenicity of varicella-zoster virus (VZV; IC₅₀ = 0.86-7 µg/ml), but was inactive against HIV-1, HIV-2, herpes simplex virus type 1 (HSV-1), vaccinia virus, vesicular stomatitis virus, respiratory syncytial virus and parainfluenza 3 virus. Other related imidazo[1,2-*a*]pyridines include the following:



Compound	R1	R2	A	Formula
270828	Me	H	-(CH ₂) ₂ -	C ₁₇ H ₁₈ N ₂ S
270830	H	Me	-CH ₂ -	C ₁₆ H ₁₆ N ₂ S

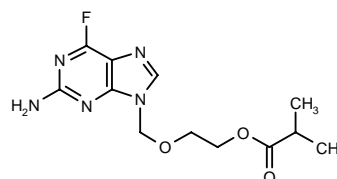
SOURCE – Rega Institute for Medical Research, Leuven (BE).

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1. Gueiffier, A. et al. *Synthesis of imidazo[1,2-*a*]pyridines as antiviral agents*. *J Med Chem* 1998, 41(25): 5108.

271556

2-Methylpropionic acid 2-(2-amino-6-fluoro-9*H*-purin-9-ylmethoxy)ethyl ester



C₁₂ H₁₆ F N₅ O₃; Mol wt: 297.2884

M.p. 85.3-7.1 °C.

ACTION – Antiviral agent, a prodrug of aciclovir that affords high oral mean urinary recovery of aciclovir (51% vs. 50% for valaciclovir) in rats. It shows good stability at pH 6.0-8.0 and sufficient solubility in aqueous solution. In mice, compound provided dose-dependent protection (100-400 mg/kg p.o.) against mortality induced by herpes simplex virus type 1 (HSV-1) infection, exhibiting comparable antiviral efficacy to valaciclovir (mean survival = 14.6 ± 3.1 days at 400 mg/kg vs. 12.0 ± 5.7 days at the same dose of valaciclovir and 6.7 ± 1.4 days in untreated controls).

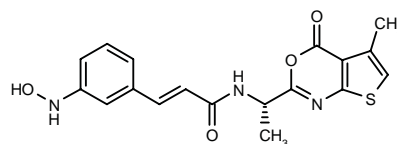
SOURCE – SK Chemicals.

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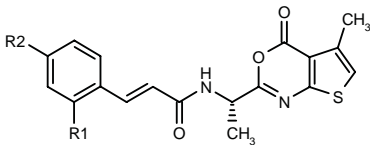
271902

3-[3-(Hydroxyamino)phenyl]-*N*-[1(*S*)-(5-methyl-4-oxo-4*H*-thieno[2,3-*d*][1,3]oxazin-2-yl)ethyl]-2(*E*)-propanamide



C₁₈ H₁₇ N₃ O₄ S; Mol wt: 371.4153

ACTION – Antiviral agent for the treatment of infections caused by herpesviruses, particularly cytomegalovirus (CMV) and herpes simplex virus type 2 (HSV-2), that acts by inhibiting herpesvirus protease (IC₅₀ < 2 µM against CMV protease). Other specifically claimed compounds within this series of thienoxazinone derivatives include the following:



Compound	R1	R2	Formula
271903	NHOH	H	C ₁₈ H ₁₇ N ₃ O ₄ S
271904	H	NHOH	C ₁₈ H ₁₇ N ₃ O ₄ S

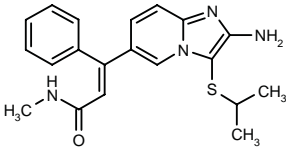
SOURCE – SmithKline Beecham.

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1. Haigh, D. et al. (SmithKline Beecham plc) *Thienoxazinone derivs. as antiviral agents*. WO 9854192.

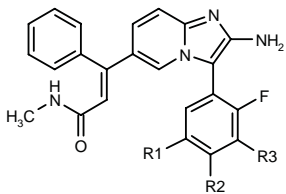
272060

3-[2-Amino-3-(isopropylsulfanyl)imidazo[1,2-*a*]pyridin-6-yl]-*N*-methyl-3-phenyl-2(*E*)-propenamide



C20 H22 N4 O S; Mol wt: 366.4868

ACTION – Antiviral agent active against rhinovirus (IC₅₀ = 0.17-0.21 µg/ml against HRV-14) and with low cytotoxicity (TC₅₀ = 10 µg/ml). Other compounds from this series of imidazopyridines are:



Compound	R1	R2	R3	Formula
272057	F	H	H	C ₂₃ H ₁₈ F ₂ N ₄ O
272058	H	F	F	C ₂₃ H ₁₇ F ₃ N ₄ O

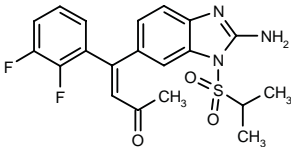
SOURCE – Lilly.

REFERENCES

1. Hamdouchi, C. et al. *2-Amino-3-substituted-6-[(E)-1-phenyl-2-(N-methylcarbamoyl)-vinyl]imidazo[1,2-a]pyridines as a novel class of inhibitors of human rhinovirus: Stereospecific synthesis and antiviral activity*. J Med Chem 1999, 42(1): 50.

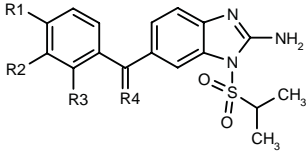
273343

4-[2-Amino-1-(isopropylsulfonyl)-1*H*-benzimidazol-6-yl]-4-(2,3-difluorophenyl)-3(*E*)-buten-2-one



C20 H19 F2 N3 O3 S; Mol wt: 419.4501

ACTION – Antiviral agent for the treatment of infections caused by picornaviruses including rhinoviruses, enteroviruses, coxsackieviruses and echoviruses, as well as flaviviruses such as hepatitis C virus (HCV) and bovine viral diarrhea virus. *In vitro*, it displayed antiviral activity in HeLa cells inoculated with HRV-14 (IC₅₀ = 0.048 µg/ml). A representative compound from a series of benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
273344	H	F	F	-(E)-CH(SO2Me)-	C ₁₉ H ₁₉ F ₂ N ₃ O ₄ S ₂
273345	H	F	F	-(E)-CH(SMe)-	C ₁₉ H ₁₉ F ₂ N ₃ O ₂ S ₂
273346	H	F	F	-(E)-CH(SOMe)-	C ₁₉ H ₁₉ F ₂ N ₃ O ₃ S ₂
273347	H	F	F	-(E)-CH(CO2Me)-	C ₂₀ H ₁₉ F ₂ N ₃ O ₄ S
273348	H	F	F	-(E)-N(OH)-	C ₁₇ H ₁₆ F ₂ N ₄ O ₃ S
273349	F	H	H	-(E)-CH(Ac)-	C ₂₀ H ₂₀ FN ₃ O ₃ S

SOURCE – Lilly.

REFERENCES

1. Dunlap, S.E. et al. (Eli Lilly and Company) *Anti-viral cpds*. WO 9855120.

NIH-351

259651

d[A-(2'→5')-A-(2'→5')-A-(2'→5')-A(oxyphosphinicooxy-1,4-butanediyl-oxyphosphinicooxy-1,4-butanediyl-oxyphosphinicooxy)-(2'→5')-A-sp-A-sp-A-sp-A-A-T-G-G-G-G-C-A-A-A-sp-T-sp-A-sp-A]DNA, 5'-(dihydrogen phosphorothioate)

sp5'A2'(p5'A2')₃-O(CH₂)₄OpO(CH₂)₄Op5'-d(AsAs-AsAATGGGGCAAAsTsAsA)

MP-351

ACTION – Antiviral agent, a 2-5A-antisense chimera targeting the respiratory syncytial virus (RSV) genome RNA, with 80-100 times greater activity than ribavirin against RSV replication *in vitro* using a variety of RSV strains including both A and B subgroup strains (EC₅₀ = 0.1-1 µM), and relatively low cytotoxicity (IC₅₀ = 2.0 µM or more). It is being developed as an aerosol formulation for the treatment of RSV. 2-5A antisense compounds combine the 2'-5' oligoadenylate molecule to standard antisense compounds to enhance the efficacy of the latter through the activation of RNase L, an enzyme that selectively destroys genetic targets.

SOURCE – Atlantic Pharmaceuticals.

REFERENCES

1. Barnard, D.L. et al. *Potent inhibition of respiratory syncytial viruses (RSV) by a 2-5A-antisense oligonucleotide chimera targeted to intragenic signals in the RSV genome*. Antivir Res 1998, 37(3): Abst 115.

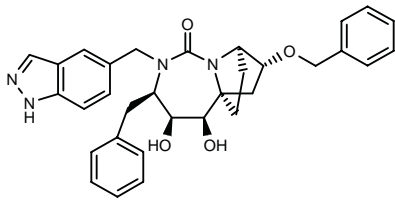
2. Player, M.R. et al. *Potent inhibition of respiratory syncytial virus replication using a 2-5A-antisense chimera targeted to signals within the virus genomic RNA*. Proc Natl Acad Sci USA 1998, 95(15): 8874.

3. *Antisense-based drug highly effective for eradicating RSV.* DailyDrugNews.com (Daily Essentials) 1997, March 6.
4. *Atlantic's 2-5A antisense compound shows excellent anti-RSV activity in vitro.* DailyDrugNews.com (Daily Essentials) 1998, April 21.
5. *Atlantic's 2-5A antisense compound targets telomerase.* DailyDrugNews.com (Daily Essentials) 1998, Feb 9.
6. *Atlantic's 2-5A improves efficacy of antisense compounds.* DailyDrugNews.com (Daily Essentials) 1997, Oct 24.
7. *Encouraging results from preclinical trial of Atlantic's RSV therapy.* DailyDrugNews.com (Daily Essentials) 1997, April 11.
8. *Second-generation 2-5A antisense drug with broad-spectrum anti-RSV activity.* DailyDrugNews.com (Daily Essentials) 1997, Dec 2.

AIDS MEDICINES

271206

(3*R*,4*S*,5*R*,5*aS*,7*R*,8*R*)-3-Benzyl-7-benzyloxy-4,5-dihydroxy-2-(1*H*-indazol-5-ylmethyl)perhydro-5*a*,8-ethanopyrrolo[1,2-*c*][1,3]diazepin-1-one



C32 H34 N4 O4; Mol wt: 538.6446

ACTION – HIV-1 protease inhibitor with a tricyclic urea core structure and nanomolar enzyme-inhibitory activity (K_i = 9 nM).

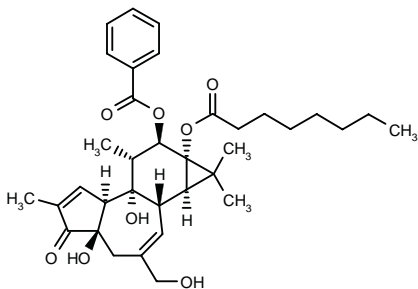
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Han, W. et al. *Tricyclic ureas: A new class of HIV-1 protease inhibitors.* Bioorg Med Chem Lett 1998, 8(24): 3615.

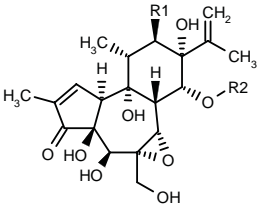
271679

Benzoic acid (1*aR*,1*bS*,4*aR*,7*aS*,7*bS*,8*R*,9*R*,9*aS*)-4*a*,7*b*-dihydroxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-9*a*-(octanoyloxy)-5-oxo-1*a*,1*b*,4,4*a*,5,7*a*,7*b*,8,9,9*a*-decahydro-1*H*-cyclopropa[3,4]benz[1,2-*e*]azulen-9-yl ester



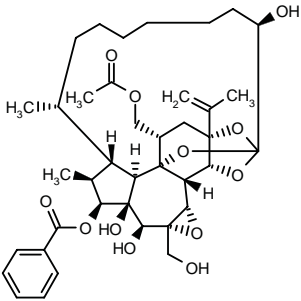
C35 H46 O8; Mol wt: 594.7404

ACTION – Antiviral agent for AIDS obtained from *Stellera chamaejasme* or *Daphne genkwa*, with potent *in vitro* activity against HIV-1 in infected MT-4 cells (EC_{50} = 0.041 ng/ml) and low cytotoxicity against uninfected cells (CC_{50} = 4.8 μ g/ml). Reported to exhibit relatively low carcinogenesis-promoting activity. Within this series of diterpene derivatives, the following are also included:

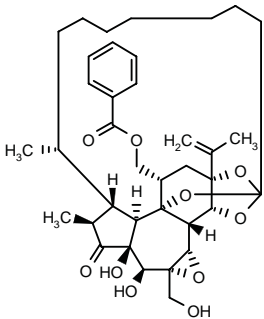


Compound	R1	R2	Formula
271680	OAc	CH=CHCH=CH(CH2)9Me	C ₃₆ H ₅₄ O ₁₀
271683	H	COCH=CHCH=CH(CH2)9Me	C ₃₅ H ₅₂ O ₉

271681: C39 H52 O12



271682: C37 H48 O10

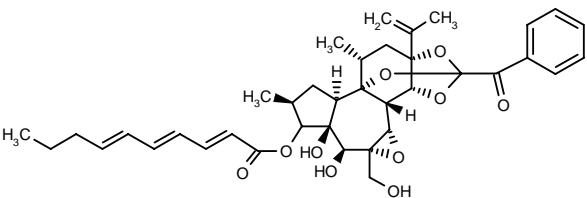


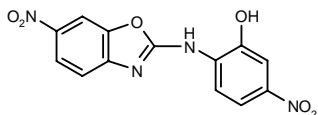
271684: C38 H46 O10

SOURCE – Tsumura.

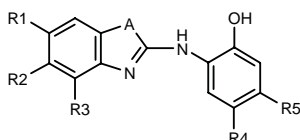
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1. Endo, Y. et al. (Tsumura & Co.) *Novel diterpenes and antiviral agents containing them.* JP 98287617.

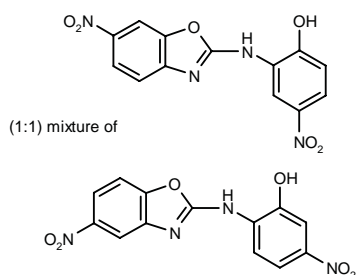
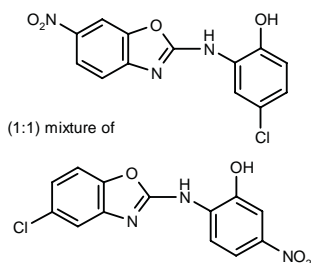
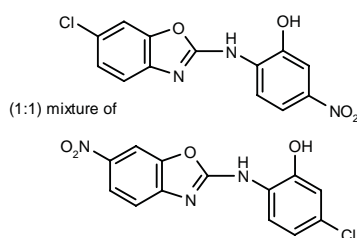


271840**5-Nitro-2-(6-nitrobenzoxazol-2-ylamino)phenol**C₁₃ H₈ N₄ O₆; Mol wt: 316.2282

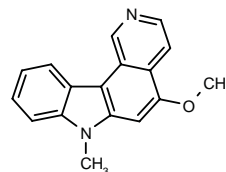
ACTION – Agent for the treatment of AIDS, autoimmune diseases such as systemic lupus erythematosus and allergic disorders, an inhibitor of cytokine production, particularly IL-4 and IL-5 production in murine lymph node cells (IC₅₀ = 0.5 μM). Other heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
271841	NO2	H	H	H	NO2	-NH-	C ₁₃ H ₉ N ₅ O ₅
271842	NO2	H	H	H	NO2	-S-	C ₁₃ H ₈ N ₄ O ₅ S
271844	H	Cl	H	NO2	H	-O-	C ₁₃ H ₈ ClN ₅ O ₄
271846	Cl	H	Cl	H	NO2	-S-	C ₁₃ H ₇ Cl ₂ N ₅ O ₅ S
271847	Cl	H	H	H	NO2	-S-	C ₁₃ H ₈ ClN ₅ O ₅ S
271848	H	Cl	H	Cl	H	-O-	C ₁₃ H ₈ Cl ₂ N ₂ O ₂
271850	Cl	H	H	H	Cl	-O-	C ₁₃ H ₈ Cl ₂ N ₂ O ₂
271851	Cl	H	H	NO2	H	-O-	C ₁₃ H ₈ ClN ₅ O ₄

**271843:** C₂₆ H₁₆ N₈ O₁₂**271845:** C₂₆ H₁₆ Cl₂ N₆ O₈**271849:** C₂₆ H₁₆ Cl₂ N₆ O₈**SOURCE** – Sumitomo Pharmaceuticals.**REFERENCES**

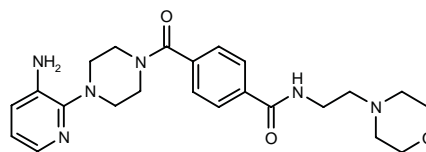
1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Heterocyclic cpds.* JP 98330369.

271990**7-Methyl-5-methoxy-7H-pyrido[4,3-c]carbazole**C₁₇ H₁₄ N₂ O; Mol wt: 262.3106

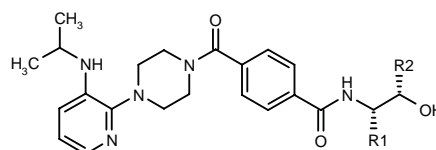
ACTION – Potent anti-HIV agent derived from mukonal, a natural extract from Rutaceous plants; it exhibited potent anti-HIV activity in acutely infected H9 lymphocytes (EC₅₀ = 5.4 ng/ml), being about 2-fold more active than zidovudine (AZT). Owing to its low cytotoxicity (IC₅₀ = 2.7 μg/ml in uninfected H9 cells), it has a therapeutic index of 503, more than 10-fold higher than that of AZT.

SOURCE – Biotech Research Laboratories.**REFERENCES**

1. Hirata, K. et al. *Substituted 7H-pyrido[4,3-c]carbazoles with potent anti-HIV activity.* Bioorg Med Chem Lett 1999, 9(2): 119.

272087**4-[4-(3-Amino-2-pyridinyl)-1-piperazinylcarbonyl]-N-[2-(4-morpholinyl)ethyl]benzamide**C₂₃ H₃₀ N₆ O₃; Mol wt: 438.5290

ACTION – Antiviral agent with particularly good activity against HIV and hepatitis B virus (HBV); it acts by inhibiting reverse transcriptase, giving 65 and 59% inhibition of HBV and HIV RT, respectively, at 0.1 μg/ml. It shows low cytotoxic potential in uninfected cells (CC₅₀ = 200 μM or more in HepG2 cells). Within this series of terephthalamide derivatives, the following are also included:



Compound	R1	R2	Formula
272088	Ph	H	C ₂₈ H ₃₃ N ₅ O ₃
272089	Me	H	C ₂₃ H ₃₁ N ₅ O ₃
272090	H	Me	C ₂₃ H ₃₁ N ₅ O ₃

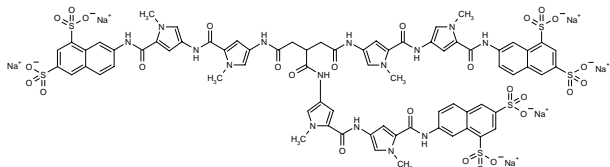
SOURCE – Dong-Wha.

REFERENCES

1. Yoon, S.J. et al. (Dong-Wha Pharmaceuticals Industry Co. Ltd) *Novel terephthalamide derivs.* WO 9854140.

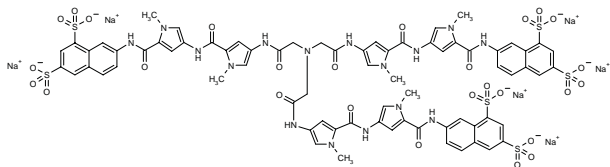
272199

N,N',N''-(Propane-1,2,3-triyl)tris(carbonyl)tris[5-[*N*-[5-[*N*-(6,8-disulfonaphthalen-2-yl)carbamoyl]-1-methylpyrrol-3-yl]carbamoyl]-1-methylpyrrol-3-amine] hexasodium salt



C72 H59 N15 Na6 O27 S6 ; Mol wt: 1896.6720

ACTION – Angiogenesis inhibitor, as demonstrated in the chorioallantoic membrane test, with potential in the treatment of disorders where the growth of new blood vessels is detrimental such as chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In addition, compound is reported to be endowed with tumor necrosis factor- α (TNF- α)-inhibitory activity and antiviral activity against lentiviruses, in particular against HIV. Another compound from this series of poly-branched polycarboxamido derivatives is:



272200: C72 H60 N16 Na6 O27 S6

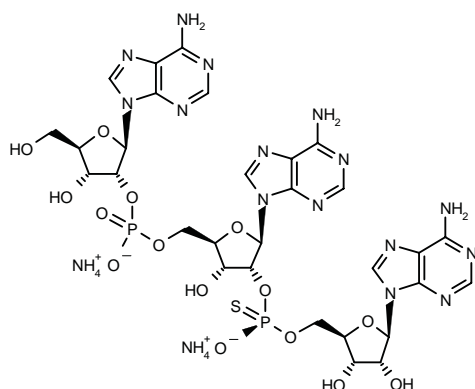
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Mongelli, N. et al. (Pharmacia & Upjohn SpA) *Poly-branched polycarboxamido cpds.* WO 9900364.

272223

Adenylyl-(2'→5')(S_P)-*P*-thioadenylyl-(2'→5')adenosine diammonium salt



C30 H37 N15 O15 P2 S . 2 H3 N; Mol wt: 975.7877

ACTION – Antiviral agent for AIDS, a synthetic analogue of naturally occurring antiviral 2',5'-oligoadenylates with greatly improved metabolic stability and antiviral activity, as demonstrated by inhibition of HIV-1-induced syncytia formation in peripheral blood lymphocytes (78% inhibition at 300 μ M), as well as HIV-1 reverse transcriptase-inhibitory activity (78% inhibition at 300 μ M).

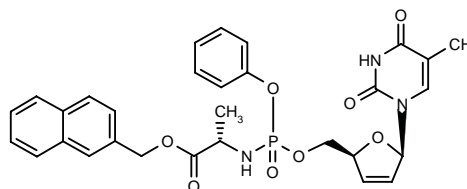
SOURCE – Temple University, Philadelphia, PA (US).

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1. Suhadolnik, R.J. and Pfeleiderer, W. (Temple University) *2',5'-Phosphorothioate/phosphodiester oligoadenylates and anti-viral uses thereof.* EP 777485, US 5863905, WO 9608256.

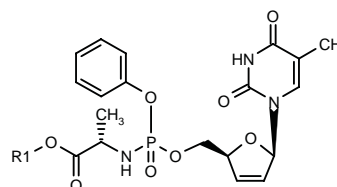
272323^{2,3}

3'-Deoxy-2',3'-didehydro-5'-O-[(*O*-2-naphthylmethyl-L-alanino)(phenoxy)phosphoryl]thymidine



C30 H30 N3 O8 P; Mol wt: 591.5540

ACTION – Anti-HIV agent, a phosphoramidate derivative of the nucleoside analogue stavudine (d4T) that acts as membrane-soluble nucleoside prodrug. In HIV-1- and HIV-2-infected human CEM cells and in HIV-2-infected thymidine kinase-deficient CEM cells, compound showed high anti-HIV activity with EC₅₀ values of 0.01, 0.04 and 0.03 μ M, respectively; it was generally more active than d4T (EC₅₀ = 0.36, 0.27 and 25 μ M, respectively). Compound also exhibited antiviral activity against murine sarcoma virus (MSV) in infected murine C3H/3T3 cells (EC₅₀ = 0.58 μ M). Relatively low cytotoxicity was observed in both CEM (CC₅₀ = 20 μ M) and in C3H/3T3 cells (CC₅₀ > 100 μ M). Other related compounds include the following:



Compound	R1	Formula
272324 ²	Ph	C ₂₅ H ₂₆ N ₃ O ₈ P
272325 ^{1,2}	CH ₂ Ph	C ₂₆ H ₂₈ N ₃ O ₈ P
272326 ²	1-Naph-CH ₂	C ₃₀ H ₃₀ N ₃ O ₈ P

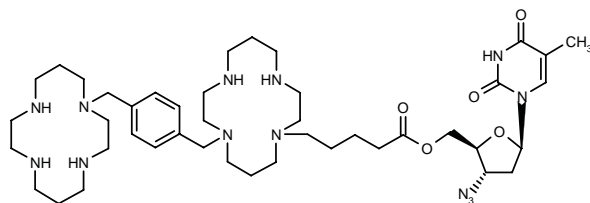
SOURCE – Rega Institute for Medical Research, Leuven (BE).

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1. McGuigan, C. et al. *Phosphoramidate derivatives of d4T with improved anti-HIV efficacy retain full activity in thymidine kinase-deficient cells.* Bioorg Med Chem Lett 1996, 6(10): 1183.
2. McGuigan, C. et al. *Synthesis, anti-human immunodeficiency virus activity and esterase lability of some novel carboxylic ester-modified phosphoramidate derivatives of stavudine (d4T).* Antivir Chem Chemother 1998, 9(6): 473.
3. Naesens, L. et al. *Metabolism and anti-HIV activity of phosphoramidate derivatives of D4T-MP with variations in the amino acid moiety.* Adv Exp Med Biol 1998, 431: 753.

272397

3'-Azido-3'-deoxythymidine 5'-[11-[[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenyl]methyl]-1,4,8,11-tetraazacyclotetradecane-1-pentanoate]



C43 H73 N13 O5; Mol wt: 852.1357

White solid.

ACTION – Anti-HIV agent, a conjugate of a bicyclam (fusion inhibitor) and zidovudine (AZT; reverse transcriptase inhibitor) shown to potently inhibit syncytia formation in HIV-infected MT-4 cells ($EC_{50} = 0.005 \mu M$ vs. 0.05 - $0.01 \mu M$ for AZT), with low cytotoxicity ($CC_{50} = 75 \mu M$; $SI = 15,000$). It exhibited a partition coefficient higher than that of AZT, suggesting greater diffusion into cells, and it was also highly stable in human plasma (half-life = 8 h). The conjugate exhibited high binding affinity for the CXCR4 coreceptor that mediates the entry of T-trophic HIV into cells. Compound probably acts as a prodrug that delivers AZT into the cell at high concentrations after fixation to the cell surface.

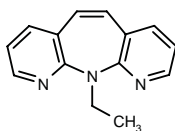
SOURCE – INSERM.

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1. Dessolin, J. et al. *New bicyclam-AZT conjugates: Design, synthesis, anti-HIV evaluation, and their interaction with CXCR-4 coreceptor.* J Med Chem 1999, 42(2): 229.

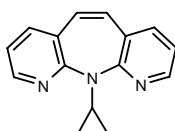
272629

11-Ethyl-11*H*-dipyrido[2,3-*b*:3',2'-*f*]azepine



C14 H13 N3; Mol wt: 223.2777

ACTION – Antiviral agent for AIDS, a non-nucleoside HIV-1 reverse transcriptase (RT) inhibitor proven effective against both wild-type and mutant HIV-1 RTM when tested *in vitro* at $1 \mu M$, it gave 98% inhibition of wild-type RT and 53, 81, 73 and 99% inhibition, respectively, of mutant Y181C, L100I, K103N and P263L RT. Another specifically claimed compound from this series of dipyrido-[2,3-*b*:3',2'-*f*]azepines is:



272630: C15 H13 N3

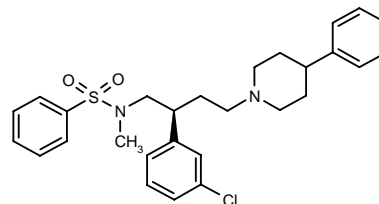
SOURCE – Boehringer Ingelheim.

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1. Proudfoot, J.R. and Dyatkin, A.B. (Boehringer Ingelheim Pharmaceuticals Inc.) *Dipyrido[2,3-*b*:3',2'-*f*]azepines and their use in the prevention or treatment of HIV infection.* US 5869482.

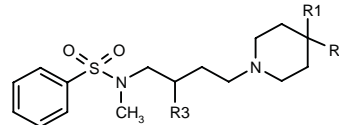
272956

N-[2(*S*)-(3-Chlorophenyl)-4-(4-phenyl-1-piperidinyl)butyl]-*N*-methylbenzenesulfonamide



C28 H33 Cl N2 O2 S; Mol wt: 497.0997

ACTION – Modulator of chemokine receptors such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR5, CXCR3 and/or CXCR4 with potential in the treatment or prevention of certain inflammatory and immunoregulatory diseases such as asthma and allergic diseases, autoimmune diseases such as rheumatoid arthritis and atherosclerosis, and preferably in the treatment or prevention of HIV infection/AIDS. Within this series of piperidine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
272957	NHCON(Me)2	H	Ph	C ₂₅ H ₃₈ N ₄ O ₃ S
272958	2-oxo-perhydro-1-benzimidazolyl	H	(S)-3-Cl-Ph	C ₂₉ H ₃₉ ClN ₄ O ₃ S
272959	Ph	OH	(S)-3-Cl-Ph	C ₂₈ H ₃₃ ClN ₂ O ₃ S
272960	CON(Me)2	Ph	Ph	C ₃₁ H ₃₉ N ₃ O ₃ S
272961	CONH2	Ph	Ph	C ₂₉ H ₃₅ N ₃ O ₃ S
272962	Ph	CH2OH	Ph	C ₂₉ H ₃₆ N ₂ O ₃ S
272963	CONHC5H11	H	Ph	C ₂₈ H ₄₁ N ₃ O ₃ S
272964	Ph	H	4-F-3-Me-Ph	C ₂₉ H ₃₅ FN ₂ O ₂ S
272965	Ph	H	2-thienyl	C ₂₆ H ₃₂ N ₂ O ₂ S ₂
272966	Ph	Ph	(S)-3-Cl-Ph	C ₃₄ H ₃₇ ClN ₂ O ₂ S
272967	4-Cl-Ph	OH	(S)-3-Cl-Ph	C ₂₈ H ₃₂ Cl ₂ N ₂ O ₃ S

SOURCE – Merck & Co.

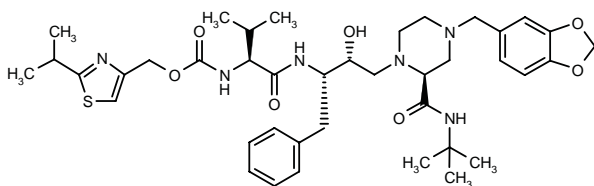
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A-160621

271182

N-(2-Isopropylthiazol-4-ylmethoxycarbonyl)-L-valine *N*-[3-[4-(1,3-benzodioxol-5-ylmethyl)-2(*S*)-(tert-butylcarbamoyl)piperazin-1-yl]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-amide



C40 H56 N6 O7 S; Mol wt: 764.9834

ACTION – Potent anti-HIV agent, an inhibitor of HIV protease (60% inhibition at 0.5 nM) with anti-HIV activity (EC_{50} = 0.007 μ M in the absence of human serum and 0.040 μ M in the presence of human serum) in HIV-infected MT-4 cells 10-20-fold greater than ritonavir (EC_{50} = 0.07 and 0.81 μ M, respectively) and relative low cytotoxicity ($CCIC_{50}$ = 13 μ M). Compound was also active against ritonavir-resistant, multiply mutated HIV clinical isolates (EC_{50} = 10-33 nM). After coadministration to rats of A-160621 and ritonavir (equal oral doses of 5 mg/kg and 10 mg/kg), the plasma levels of compound were elevated 6-24-fold, the plasma levels of A-160621 exceeding the EC_{50} in the presence of human serum even after 8 h.

SOURCE – Abbott.

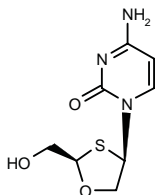
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BCH-10652*

190708

(*R,R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-4-yl]cytosine
dOTC



C8 H11 N3 O3 S; Mol wt: 229.2589

ACTION – Nucleoside reverse transcriptase inhibitor (NRTI) with potent *in vitro* activity against laboratory strains and clinical isolates of HIV-1 in T-cell lines and lymphocytes (IC_{50} = 0.08-4.8 μ M); compound also showed efficacy against clinical isolates resistant to other RT inhibitors such as zidovudine and lamivudine. Additive or slight synergistic effects were obtained when compound was combined with other nucleoside analogues, non-nucleoside RT inhibitors such as nevirapine or protease inhibitors. Pharmacokinetic studies in healthy volunteers indicated that single oral doses of 1600 are well tolerated and absorbed, with a long plasma half-life suggesting the

feasibility of once- or twice-daily dosing.

SOURCE – BioChem Pharma.

REFERENCES

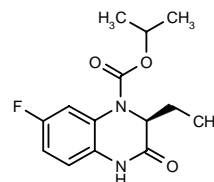
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 - Rando, R.F. et al. Antiretroviral activity, safety and metabolism of BCH-10652, a new nucleoside analogue. 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb 4, Chicago) 1999, Abst 595.
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 - BioChem Pharma initiates clinical testing of another AIDS drug. DailyDrugNews.com (Daily Essentials) 1998, May 7.
 - BioChem Pharma positioned for strong growth. DailyDrugNews.com (Daily Essentials) 1998, April 23.
- *Identified compound 190708 (see 186273) Drug Data Report 1993, 015(01): 0094.

GW-420867X

272215

2(*S*)-Ethyl-7-fluoro-3-oxo-1,2,3,4-tetrahydroquinoxaline-1-carboxylic acid isopropyl ester

GW-867
HBY-1293



C14 H17 F N2 O3; Mol wt: 280.2973

ACTION – Potent and selective, non-nucleoside HIV-1 reverse transcriptase inhibitor (IC_{50} = 33.5 nM) with nanomolar potency against laboratory and clinical isolates of HIV-1 in different cell types. Compound exhibited additive or synergistic effects in combination with other non-nucleoside RT inhibitors or protease inhibitors and did not show cytotoxic or cytostatic effects in different cell systems over the range of 40-100 μ g/ml. In healthy male volunteers, compound was generally well tolerated up to 900 mg and showed favorable oral pharmacokinetics. GW-420867 is currently undergoing phase II trials in HIV-infected patients.

SOURCES – Bayer; Hoechst Marion Roussel; licensed to Glaxo Wellcome.

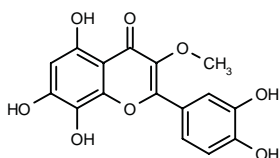
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6. Prince, W. et al. *GW420867X, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) - Initial phase I evaluation*. Antivir Res 1999, 41(2): Abst 49.
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NSC-618929

272322

2-(3,4-Dihydroxyphenyl)-5,7,8-trihydroxy-3-methoxy-4H-1-benzopyran-4-one



C16 H12 O8; Mol wt: 332.2628

ACTION – An inhibitor of HIV-1 integrase ($IC_{50} = 0.7 \mu M$ for both 3'-processing and integration) with no antiviral activity in HIV-1-infected CEM cells; its cytotoxic concentration ($CC_{50} = 15.7 \mu M$) was considerably lower than the IC_{50} for integrase. A potential lead compound for the development of potent integrase inhibitors.

SOURCE – National Cancer Institute, Bethesda, MD (US).

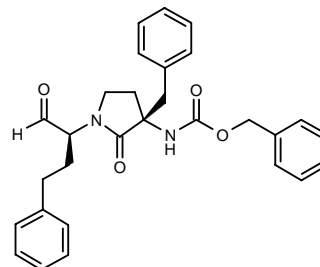
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TREATMENT OF PROTOZOAL DISEASES

271549

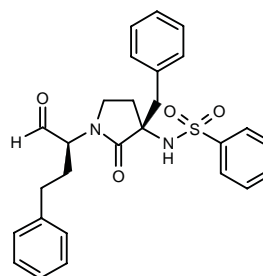
N-[3(*S*)-Benzyl-1-[1(*S*)-formyl-3-phenylpropyl]-2-oxo-pyrrolidin-3-yl]carbamic acid benzyl ester



C29 H30 N2 O4; Mol wt: 470.5660

Clear oil, $[\alpha]_D^{26} +40.3^\circ$ (c 0.3, CH_2Cl_2).

ACTION – Antiprotozoal agent, a cysteine protease inhibitor with submicromolar activity against the major *Trypanosoma cruzi* protease cruzain ($IC_{50} = 0.6 \mu M$) and the major cathepsin B-like protease from *Leishmania major* ($IC_{50} = 0.03 \mu M$). Potentially useful for the therapy of parasitic diseases such Chagas' disease and leishmaniasis. Another compound from this series of conformationally constrained γ -lactams is:



271553: C27 H28 N2 O4 S

SOURCES – Indiana University, Indianapolis, IN (US); University of Michigan, Ann Arbor, MI (US).

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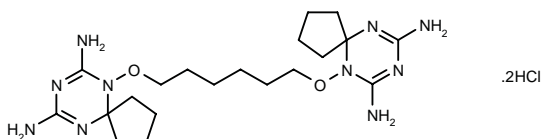
TRYBIZINE HYDROCHLORIDE

269255

1',1''-(Hexamethylenedioxy)bis(spiro[cyclopentane-1,2'(1'H)-1',3',5'-triazine]-4',6'-diamine) dihydrochloride

SIPI-1029

T-46



C₂₀ H₃₆ N₁₀ O₂ · 2HCl; Mol wt: 521.4942

ACTION – Antitrypanosomal agent with strong *in vitro* activity against *Trypanosoma brucei* subsp. *rhodesiense*, *T. brucei gambiense* and *T. brucei brucei* (MIC = 0.4, 2.7 and 2.6 ng/ml, respectively), and also active against multidrug-resistant *T. brucei brucei* (MIC = 28 ng/ml); however, it was inactive against the intracellular parasites *Trypanosoma cruzi* and *Leishmania donovani*. No cytotoxicity was observed against mammalian cells. In mice infected with *T. brucei* subsp. *rhodesiense* and *T. brucei gambiense*, it completely eliminated the infection after 4 i.p. doses of 0.25 or 1 mg/kg, as well as after 4 oral doses of 20 mg/kg, but it was not able to cure infections caused by multidrug-resistant *T. brucei* subsp. *brucei*. Compound alone was not curative against late-stage CNS infection caused by *T. brucei* subsp. *brucei*, but cure rates of 33-80% were obtained on different dosing schedules when it was coadministered with noncurative doses of difluoromethylornithine (DFMO).

SOURCE – Shanghai Institute of Pharmaceutical Industry, Shanghai (CN).

REFERENCES

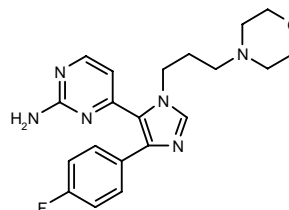
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2. Bacchi, C.J. et al. *Antitrypanosomal activity of a new triazine derivative, SIPI 1029, in vitro and in model infections*. *Antimicrob Agents Chemother* 1998, 42(10): 2718.
3. Brun, R. and Kaminsky, R. *In vitro and in vivo activities of trybizine hydrochloride against various pathogenic trypanosome species*. *Antimicrob Agents Chemother* 1998, 42(11): 2858.
4. Zhou, W.C. et al. *Synthesis and antiprotozoal activities of some new triazine derivatives including a new antitrypanosomal agent: SIPI-1029*. *Acta Pharm Sin* 1996, 31(11): 823.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

270649

4-[4-(4-Fluorophenyl)-1-[3-(4-morpholinyl)propyl]-1*H*-imidazol-5-yl]pyrimidin-2-amine



C₂₀ H₂₃ F N₆ O; Mol wt: 382.4407

ACTION – Potential antiinflammatory agent, a pyrimidinylimidazole inhibitor of p38/CSBP MAP kinase (IC₅₀ = 0.48 μM) with significantly reduced inhibitory activity against cytochrome P-450. *In vivo*, orally administered compound showed significant inhibition of the lipopolysaccharide (LPS)-induced increase in serum tumor necrosis factor (TNF-α) levels in mice and was more active than the reference compound SB-210313 (ED₅₀ = 5.2 and 42 mg/kg, respectively).

This kinase has been suggested to be an attractive target for the development of agents for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

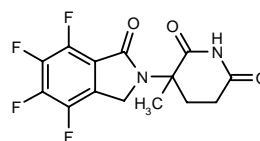
SOURCE – SmithKline Beecham.

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4. Adams, J.L. et al. (SmithKline Beecham plc) *Tri-substd. imidazoles having multiple therapeutic properties*. EP 708768, WO 9502591.
5. Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries*. EP 889888, WO 9735856.
6. Adams, J.L. et al. *Pyrimidinylimidazole inhibitors of CSBP/p38 kinase demonstrating decreased inhibition of hepatic cytochrome P450 enzymes*. *Bioorg Med Chem Lett* 1998, 8(22): 3111.

271859

3-Methyl-3-(4,5,6,7-tetrafluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione



C₁₄ H₁₀ F₄ N₂ O₃; Mol wt: 330.2360

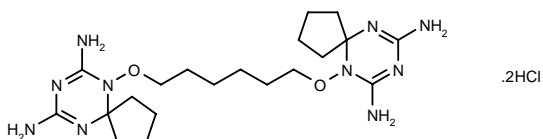
TRYBIZINE HYDROCHLORIDE

269255

1',1''-(Hexamethylenedioxy)bis(spiro[cyclopentane-1,2'(1'*H*)-1',3',5'-triazine]-4',6'-diamine) dihydrochloride

SIPI-1029

T-46



C20 H36 N10 O2 . 2HCl; Mol wt: 521.4942

ACTION – Antitrypanosomal agent with strong *in vitro* activity against *Trypanosoma brucei* subsp. *rhodesiense*, *T. brucei gambiense* and *T. brucei brucei* (MIC = 0.4, 2.7 and 2.6 ng/ml, respectively), and also active against multidrug-resistant *T. brucei brucei* (MIC = 28 ng/ml); however, it was inactive against the intracellular parasites *Trypanosoma cruzi* and *Leishmania donovani*. No cytotoxicity was observed against mammalian cells. In mice infected with *T. brucei* subsp. *rhodesiense* and *T. brucei gambiense*, it completely eliminated the infection after 4 i.p. doses of 0.25 or 1 mg/kg, as well as after 4 oral doses of 20 mg/kg, but it was not able to cure infections caused by multidrug-resistant *T. brucei* subsp. *brucei*. Compound alone was not curative against late-stage CNS infection caused by *T. brucei* subsp. *brucei*, but cure rates of 33-80% were obtained on different dosing schedules when it was coadministered with noncurative doses of difluoromethylornithine (DFMO).

SOURCE – Shanghai Institute of Pharmaceutical Industry, Shanghai (CN).

REFERENCES

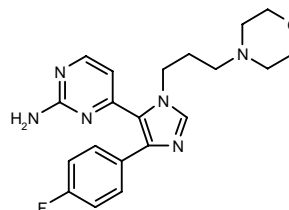
1. Zhou, W.C. et al. (Shanghai Institute of Pharmaceutical Industry) *Triazine derivs. and preparing process thereof*. CN 1096514.
2. Bacchi, C.J. et al. *Antitrypanosomal activity of a new triazine derivative, SIPI 1029, in vitro and in model infections*. *Antimicrob Agents Chemother* 1998, 42(10): 2718.
3. Brun, R. and Kaminsky, R. *In vitro and in vivo activities of trybizine hydrochloride against various pathogenic trypanosome species*. *Antimicrob Agents Chemother* 1998, 42(11): 2858.
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

270649

4-[4-(4-Fluorophenyl)-1-[3-(4-morpholinyl)propyl]-1*H*-imidazol-5-yl]pyrimidin-2-amine



C20 H23 F N6 O; Mol wt: 382.4407

ACTION – Potential antiinflammatory agent, a pyrimidinylimidazole inhibitor of p38/CSBP MAP kinase (IC₅₀ = 0.48 μM) with significantly reduced inhibitory activity against cytochrome P-450. *In vivo*, orally administered compound showed significant inhibition of the lipopolysaccharide (LPS)-induced increase in serum tumor necrosis factor (TNF-α) levels in mice and was more active than the reference compound SB-210313 (ED₅₀ = 5.2 and 42 mg/kg, respectively).

This kinase has been suggested to be an attractive target for the development of agents for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

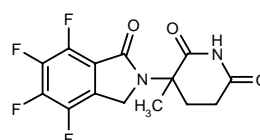
SOURCE – SmithKline Beecham.

REFERENCES

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2. Adams, J.L. et al. (SmithKline Beecham Corp.) *Pyridyl imidazole cpds. and compsns*. US 5670527.
3. Adams, J.L. et al. (SmithKline Beecham plc) *Certain 1,4,5-tri-substd. imidazole cpds. useful as cytokine*. EP 809499, JP 98512555, US 5593992, WO 9621452.
4. Adams, J.L. et al. (SmithKline Beecham plc) *Tri-substd. imidazoles having multiple therapeutic properties*. EP 708768, WO 9502591.
5. Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries*. EP 889888, WO 9735856.
6. Adams, J.L. et al. *Pyrimidinylimidazole inhibitors of CSBP/p38 kinase demonstrating decreased inhibition of hepatic cytochrome P450 enzymes*. *Bioorg Med Chem Lett* 1998, 8(22): 3111.

271859

3-Methyl-3-(4,5,6,7-tetrafluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione



C14 H10 F4 N2 O3; Mol wt: 330.2360

ACTION – Agent for the treatment of inflammatory and autoimmune diseases, an inhibitor of tumor necrosis factor (TNF- α) production and of the activity of the transcription factor NF- κ B. A representative compound within a series of substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and 1-oxo-2-(2,6-dioxopiperidin-3-yl)isoindolines.

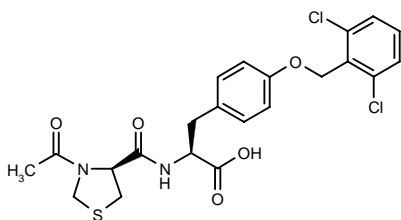
SOURCE – Celgene.

REFERENCES

1. Muller, G.W. et al. (Celgene Corp.) *Substd. 2-(2,6-dioxopiperidin-3-yl)-phthalimides and 1-oxoisoindolines and method of reducing TNF α levels.* WO 9854170.

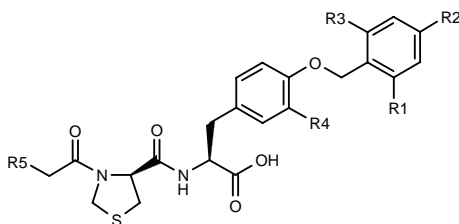
271910

N-Acetyl-4-thia-D-prolyl-[4-*O*-(2,6-dichlorobenzyl)]-L-tyrosine

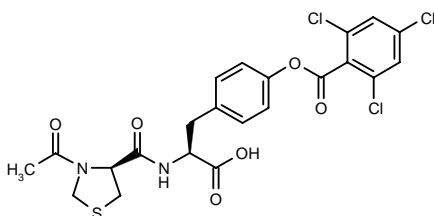


C22 H22 Cl2 N2 O5 S; Mol wt: 497.3968

ACTION – Agent for the treatment of immune or inflammatory disorders that is reported to potently and selectively inhibit the binding of α 4 integrins to their ligands, proven active in inhibiting cell adhesion mediated by α 4/ β 1 and α 4/ β 7 integrins. Other specifically claimed tyrosine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
271911	Cl	Cl	Cl	H	H	C ₂₂ H ₂₁ Cl ₃ N ₂ O ₅ S
271912	F	H	F	H	H	C ₂₂ H ₂₂ F ₂ N ₂ O ₅ S
271913	Cl	H	Cl	NO ₂	H	C ₂₂ H ₂₁ Cl ₂ N ₃ O ₇ S
271914	Cl	H	Cl	H	CO ₂ H	C ₂₃ H ₂₂ Cl ₂ N ₂ O ₇ S



271915: C22 H19 Cl3 N2 O6 S

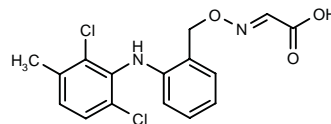
SOURCE – Celltech.

REFERENCES

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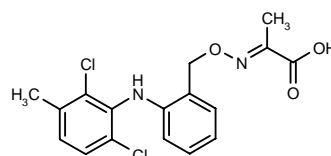
271977

2-[2-(2,6-Dichloro-3-methylphenylamino)benzyl-oxyimino]acetic acid



C16 H14 Cl2 N2 O3; Mol wt: 353.2036

ACTION – Antiinflammatory agent, an inhibitor of prostaglandin biosynthesis mainly via inhibition of cyclooxygenase type 2 (COX-2) activity (68% inhibition at 0.1 μ M using recombinant human enzyme), with relatively much less effect against COX-1 (IC₅₀ = 6 μ M using recombinant human enzyme). Another representative compound within this series of specifically claimed iminoxy derivatives of fenamates is:



271978: C17 H16 Cl2 N2 O3

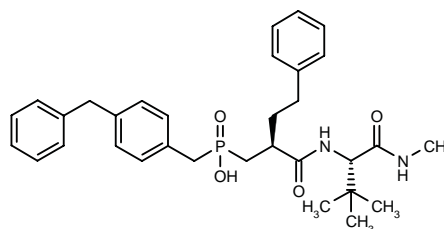
SOURCE – Abbott.

REFERENCES

1. Brooks, C.D.W. et al. (Abbott Laboratories Inc.) *Iminoxyderivs. of fenamates as inhibitors of prostaglandin biosynthesis.* US 5863946.

271992

[4-(Benzyl)benzyl][2(*S*)-[*N*-[2,2-dimethyl-1(*S*)-(*N*-methyl-carbamoyl)propyl]carbamoyl]-2-(2-phenylethyl)ethyl]-phosphinic acid



C32 H41 N2 O4 P; Mol wt: 548.6599

ACTION – Potent inhibitor of the matrix metalloproteinase MMP-13 (collagenase 3; IC₅₀ = 14 nM) with good selectivity relative to MMP-3 (stromelysin; IC₅₀ = 1200 nM) and MMP-1 (fibroblast collagenase; IC₅₀ = 690 nM). In rats, after i.v. administration it exhibited a good pharmacokinetic profile, with low clearance (12 ml/min/kg) and a terminal half-life of 2.3 h, but it was not absorbed after oral administration. SAR studies on related phosphinates are in progress to find a compound with greater potency and selectivity, as well as oral activity, as a potential therapeutic agent for conditions related to MMP overexpression and activation, such as cancer and arthritis.

SOURCE – Pfizer.

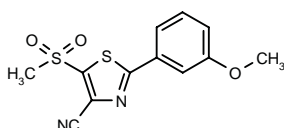
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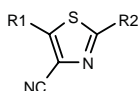
272036

2-(3-Methoxyphenyl)-5-(methylsulfonyl)thiazole-4-carbonitrile



C12 H10 N2 O3 S2; Mol wt: 294.3540

ACTION – Agent for the treatment of diseases caused by excessive production of nitric oxide (NO) such as arthritis, cerebral ischemia, Alzheimer's disease, myocarditis and arteriosclerosis that acts by inhibiting the inducible isoform of nitric oxide synthase (iNOS; IC₅₀ = 0.011 μM in mouse macrophages). Also reported to inhibit IL-6 activity. Other representative compounds within this series of thiazole derivatives include the following:



Compound	R1	R2	Formula
272039	SO ₂ Me	Ph	C ₁₁ H ₈ N ₂ O ₂ S ₂
272040	SOMe	3-MeO-Ph	C ₁₂ H ₁₀ N ₂ O ₂ S ₂
272041	SO ₂ Me	2-thienyl	C ₉ H ₆ N ₂ O ₂ S ₃
272042	i-BuSO ₂	3-MeO-Ph	C ₁₅ H ₁₆ N ₂ O ₃ S ₂

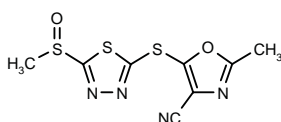
SOURCE – Takeda.

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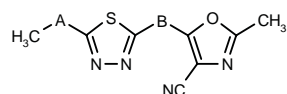
272044

2-Methyl-5-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl-sulfanyl]oxazole-4-carbonitrile



C8 H6 N4 O2 S3; Mol wt: 286.3594

ACTION – Agent for the treatment of disorders caused by excessive production of nitric oxide (NO) such as arthritis, cerebral ischemia, Alzheimer's disease, myocarditis and arteriosclerosis that acts by inhibiting the inducible isoform of nitric oxide synthase (iNOS; IC₅₀ = 0.23 μM in mouse macrophages). Compound potently inhibited the lipopolysaccharide (LPS)-induced increase in serum NO levels in mice (80% at 30 mg/kg i.p.). It also potently inhibited IL-6 production *in vitro* (IC₅₀ = 0.83 μM) and the LPS-stimulated increase in serum amyloid A protein in mice (51% at 50 mg/kg p.o.). Other representative compounds within this series ofazole derivatives include the following:



Compound	A	B	Formula
272045	SO ₂	S	C ₈ H ₆ N ₄ O ₃ S ₃
272046	SO	bond	C ₈ H ₆ N ₄ O ₂ S ₂
272047	SO ₂	bond	C ₈ H ₆ N ₄ O ₂ S ₂

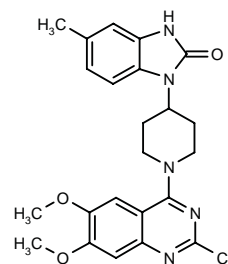
SOURCE – Takeda.

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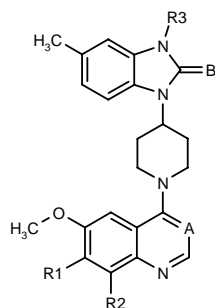
272049

1-[1-(2-Chloro-6,7-dimethoxy-4-quinazolinyl)piperidin-4-yl]-5-methyl-2,3-dihydro-1H-benzimidazol-2-one



C23 H24 Cl N5 O3; Mol wt: 453.9276

ACTION – Antiinflammatory, antiallergic and anti-metastatic agent also reported to possess immuno-suppressant activity that displays significant cell adhesion-inhibitory activity, as demonstrated *in vitro* using human umbilical vein endothelial cells (HUVEC) and HL-60 cells stimulated by tumor necrosis factor (TNF-α; 86% inhibition at 1 μM). Within this series of piperidine derivatives the following are also included:



Compound	R1	R2	R3	A	B	Formula
272050	OMe	H	H	N	S	C ₂₃ H ₂₅ N ₅ O ₂ S
272051	OMe	H	3,4-(MeO)2-PhCOCH ₂	N	O	C ₃₃ H ₃₅ N ₅ O ₆
272053	H	OMe	H	C(CO ₂ Et)	O	C ₂₇ H ₃₀ N ₄ O ₅

SOURCE – Kyowa Hakko.

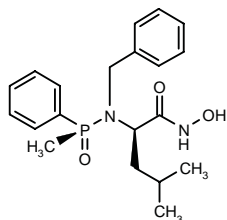
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272064

2(*R*)-[*N*-Benzyl-*N*-[(*R_p*)-(methyl)phenylphosphoryl]amino]-*N*-hydroxy-4-methylpentanamide

*N*²-Benzyl-*N*²-[(*R_p*)-(methyl)phenyl)phosphoryl]-*N*¹-hydroxy-D-leucinamide



C₂₀ H₂₇ N₂ O₃ P; Mol wt: 374.4183

White crystalline solid.

ACTION – Potent, broad-spectrum matrix metalloproteinase (MMP) inhibitor with IC₅₀ values of 20.5, 24.4, 13.3, 5.3, 20.6 and 7.4 nM, respectively, against fibroblast collagenase (MMP-1), stromelysin (MMP-3), gelatinase A (MMP-2), neutrophil collagenase (MMP-8), gelatinase B (MMP-9) and collagenase 3 (MMP-13); it was less active against matrilysin (MMP-7; IC₅₀ = 886 nM). Potentially useful for the treatment of MMP-related pathologies such as arthritis, tumor growth and metastasis, periodontal disease and multiple sclerosis.

SOURCE – Procter & Gamble.

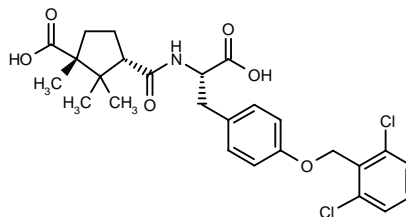
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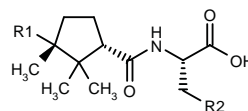
272074

N-[3(*R*)-Carboxy-2,2,3-trimethylcyclopent-1(*S*)-ylcarbonyl]-4-*O*-(2,6-dichlorobenzyl)-*L*-tyrosine



C₂₆ H₂₉ Cl₂ N O₆; Mol wt: 522.4221

ACTION – α 4/ β 1 integrin antagonist claimed for use in the treatment or prevention of α 4/ β 1 adhesion-mediated conditions such as rheumatoid arthritis, psoriasis, asthma, allergy, allograft rejection, atherosclerosis and ulcerative colitis. Compound was tested *in vitro* for its inhibitory effect on β 1-mediated Jurkat-endothelial cell adhesion (IC₅₀ < 0.8 μ M). It exhibited *in vivo* activity in a dextran pleurisy model in mice, as determined by measuring inhibition of pleural leukocyte infiltration. Other representative compounds include the following:



Compound	R1	R2	Formula
272075	CO ₂ H	1-[3,4-(Cl)2-PhCH ₂]-4-imidazolyl	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₅
272076	CO ₂ H	4-[2,6-(Cl)2-PhCONH]-Ph	C ₂₆ H ₂₈ Cl ₂ N ₂ O ₆
272077	CN	4-[2,6-(Cl)2-PhCONH]-Ph	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₄

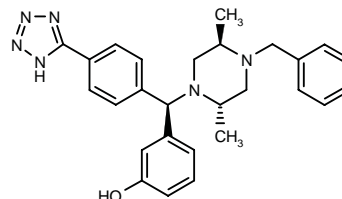
SOURCES – Pharmacia & Upjohn; Tanabe.

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1. Lobl, T.J. et al. (Tanabe Seiyaku Co., Ltd.; Pharmacia & Upjohn Co.) *Inhibitors of α 4 β 1 mediated cell adhesion.* WO 9858902.

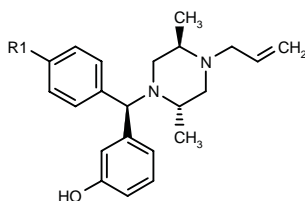
272174

(-)-3-[1(*R*)-[(2*S*,5*R*)-4-Benzyl-2,5-dimethylpiperazin-1-yl][4-(1*H*-tetrazol-5-yl)phenyl]methyl]phenol



C₂₇ H₃₀ N₆ O; Mol wt: 454.5750

ACTION – Potent and selective δ -opioid agonist (pIC₅₀ = 10.9 in mouse vas deferens) with potential in the treatment or prevention of inflammatory diseases such as arthritis, psoriasis, asthma or inflammatory bowel disease, respiratory disorders, gastrointestinal disorders and urogenital tract disorders, as well as for use as an analgesic or immunosuppressant. A representative compound from a series of piperazinylbenzyltetrazole derivatives, wherein the following are also included:



Compound	R1	Formula
272175	5-tetrazolyl	C ₂₃ H ₂₈ N ₆ O
272176	2-[CO ₂ H(CH ₂) ₄]-5-tetrazolyl	C ₂₈ H ₃₆ N ₆ O ₃

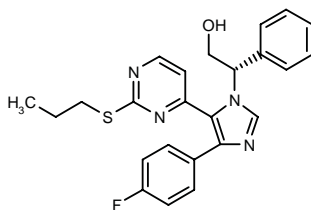
SOURCE – Pfizer.

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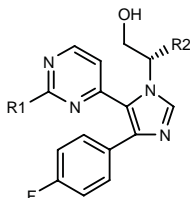
272209

2(S)-[4-(4-Fluorophenyl)-5-[2-(propylsulfanyl)pyrimidin-4-yl]-1*H*-imidazol-1-yl]-2-phenylethanol



C₂₄ H₂₃ F N₄ O S; Mol wt: 434.5367

ACTION – An inhibitor of the production of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), as well as proinflammatory proteins such as cyclooxygenase type 2 (COX-2), that acts by inhibiting CSBP/p38/RK kinase activity. Potentially useful in the treatment of a broad range of conditions including rheumatoid arthritis, osteoarthritis, septic shock, Alzheimer's disease, asthma, adult respiratory distress syndrome, osteoporosis, restenosis, reperfusion injury, cancer, graft-versus-host disease, transplant rejection, inflammatory bowel disease, multiple sclerosis and psoriasis. Other exemplified compounds from this series of 1,4,5-substituted imidazole derivatives include the following:



Compound	R1	R2	Formula
272210	OMe	Ph	C ₂₂ H ₁₉ FN ₄ O ₂
272211	NHPh	Me	C ₂₂ H ₂₀ FN ₅ O

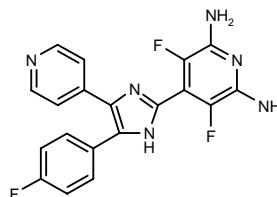
SOURCE – SmithKline Beecham.

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272212

3,5-Difluoro-4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-yl]pyridine-2,6-diamine



C₁₉ H₁₃ F₃ N₆; Mol wt: 382.3477

ACTION – An inhibitor of the production of cytokines such as tumor necrosis factor (TNF- α) and IL-1 that acts by inhibiting p38 mitogen-activated protein (MAP) kinase (IC₅₀ = 10 nM). *In vitro*, compound was shown to inhibit the release of TNF- α from human peripheral blood mononuclear cells (PBMCs) with an IC₅₀ value of about 90 nM, and it was found to inhibit TNF- α production *in vivo* in lipopolysaccharide (LPS)-stimulated mice, giving about 80% inhibition at 10 mg/kg p.o. Potentially useful for the treatment or prevention of inflammatory disorders, autoimmune diseases, bone metabolism disorders, severe infections, transplant rejection and graft-versus-host disease. A representative compound from a series of 2-substituted 4,5-diarylimidazoles.

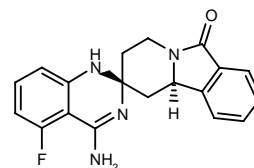
SOURCE – Novartis.

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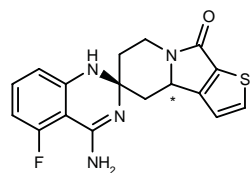
272241

(\pm)-(R*,R*)-4'-Amino-5'-fluoro-1,2,3,4,6,10b-hexahydro-spiro[pyrido[2,1-a]isoindole-2,2'(1'H)-quinazolin]-6-one



C₁₉ H₁₇ F N₄ O; Mol wt: 336.3683

ACTION – Agent for the treatment or prevention of inflammatory disorders such as rheumatoid arthritis and asthma, as well as pain, that acts by inhibiting inducible nitric oxide synthase (iNOS). Other exemplified compounds from this series of spiro derivatives include the following:



Compound	*Isomer	Formula
272242	R*	C ₁₇ H ₁₅ FN ₄ OS
272243	S*	C ₁₇ H ₁₅ FN ₄ OS

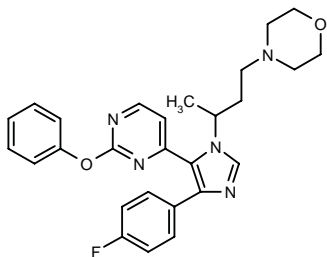
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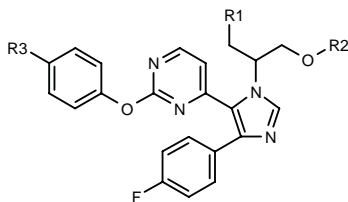
272244

4-(4-Fluorophenyl)-1-[1-methyl-3-(4-morpholinyl)propyl]-5-(2-phenoxyypyrimidin-4-yl)-1*H*-imidazole



C27 H28 F N5 O2; Mol wt: 473.5492

ACTION – An inhibitor of the production of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), as well as proinflammatory proteins such as cyclooxygenase type 2 (COX-2), that acts by inhibiting CSBP/p38/RK kinase activity. Potentially useful in the treatment of a broad range of conditions including rheumatoid arthritis, osteoarthritis, septic shock, Alzheimer’s disease, asthma, adult respiratory distress syndrome, osteoporosis, restenosis, reperfusion injury, cancer, graft-versus-host disease, transplant rejection, inflammatory bowel disease, multiple sclerosis and psoriasis. Other specifically claimed compounds from this series of 1,4,5-substituted imidazole derivatives include the following:



Compound	R1	R2	R3	Formula
272245	H	H	F	C ₂₂ H ₁₈ F ₂ N ₄ O ₂
272246	OH	H	F	C ₂₂ H ₁₈ F ₂ N ₄ O ₃
272247	H	Ph	H	C ₂₈ H ₂₃ FN ₄ O ₂
272248	Me	H	Cl	C ₂₃ H ₂₀ ClFN ₄ O ₂
272249	Me	H	Me	C ₂₄ H ₂₃ FN ₄ O ₂

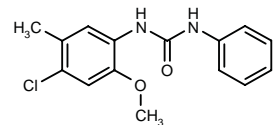
SOURCE – SmithKline Beecham.

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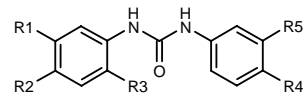
272250

*N*¹-(4-Chloro-2-methoxy-5-methylphenyl)-*N*²-phenylurea



C15 H15 Cl N2 O2; Mol wt: 290.7485

ACTION – Agent for the treatment or prevention of inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, viral diseases, ischemia/reperfusion injury in stroke, myocardial ischemia, renal ischemia, heart attack and organ hypoxia, an inhibitor of p38 (also known as CSBP and RK) kinase (IC₅₀ = 0.1 μM). Other exemplified compounds from this series of urea derivatives include the following:



Compound	R1	R2	R3	R4=R5	Formula
272251	Cl	NO2	OH	H	C ₁₃ H ₁₀ ClN ₃ O ₄
272252	Me	NO2	OMe	H	C ₁₅ H ₁₅ N ₃ O ₄
272254	Cl	Cl	H	Cl	C ₁₃ H ₆ Cl ₄ N ₂ O
272255	H	H	CONH2	Cl	C ₁₄ H ₁₁ Cl ₂ N ₃ O ₂

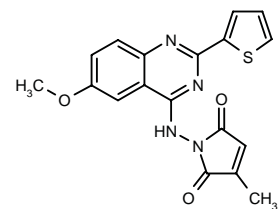
SOURCE – Vertex.

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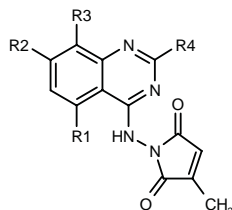
272256

1-[6-Methoxy-2-(2-thienyl)-4-quinazolinylamino]-3-methyl-2,5-dihydro-1*H*-pyrrole-2,5-dione



C18 H14 N4 O3 S; Mol wt: 366.3996

ACTION – Agent for the treatment or prevention of immunoinflammatory and autoimmune diseases, as well as for the prevention of transplant rejection, that acts by blocking the activation of transcription factors, particularly NF- κ B and AP-1, which results in a decrease in the production of proinflammatory cytokines such as IL-1, IL-2, IL-8 and/or tumor necrosis factor (TNF- α). *In vitro*, compound was found to inhibit the activation of NF- κ B and AP-1 in human Jurkat T-cells with IC₅₀ values of 0.002 and 0.003 μ M, respectively; cytokine levels were determined in the supernatants and compound was found to inhibit IL-2 and IL-8 production with IC₅₀ values of 0.0008 and 0.0005 μ M, respectively. Within this series of quinazoline derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
272257	Me	H	H	CF ₃	C ₁₅ H ₁₁ F ₃ N ₄ O ₂
272258	OMe	H	H	2-thienyl	C ₁₈ H ₁₄ N ₄ O ₃ S
272259	H	OMe	H	2-thienyl	C ₁₈ H ₁₄ N ₄ O ₃ S
272260	H	H	OMe	2-thienyl	C ₁₈ H ₁₄ N ₄ O ₃ S

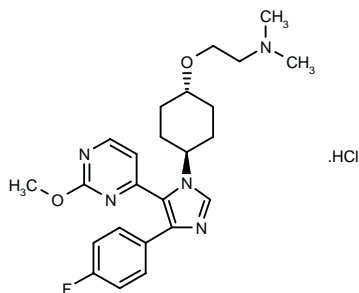
SOURCE – Signal.

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272351

trans-N-[2-[4-[4-(4-Fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)-1*H*-imidazol-1-yl]cyclohexyloxy]ethyl]-*N,N*-dimethylamine hydrochloride



C24 H30 F N5 O2 . HCl; Mol wt: 475.9929

ACTION – Agent for the treatment of cytokine-mediated diseases including arthritis and other inflammatory disorders that acts as an inhibitor of p38 MAP (mitogen-activated protein) kinase (also known as CSBP or RK kinase), thereby inhibiting the production of IL-1, IL-6, IL-8 and/or tumor necrosis factor (TNF). A specifically claimed compound within a series of cycloalkyl substituted imidazole derivatives.

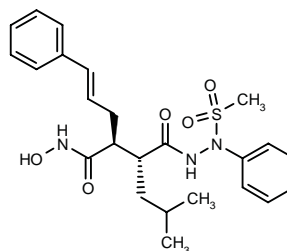
SOURCE – SmithKline Beecham.

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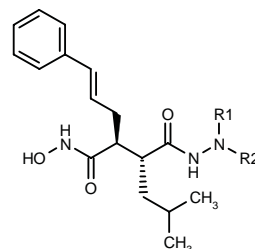
272425

2(*S*)-[3-Methyl-1(*R*)-[3-(methylsulfonyl)-3-phenylcarbazoyl]butyl]-5-phenyl-4(*E*)-pentenehydroxamic acid



C24 H31 N3 O5 S; Mol wt: 473.5909

ACTION – Antiinflammatory and antiarthritic agent that inhibits the release of tumor necrosis factor (TNF- α ; IC₅₀ = 437 nM in THP1 cells stimulated by lipopolysaccharide) and transforming growth factor- α (TGF- α ; IC₅₀ = 210 nM in NHEK cells stimulated by TPA), as well as keratinocyte proliferation (IC₅₀ = 1300 nM). Potentially useful particularly in the treatment of inflammation, fever, hemorrhage, sepsis, rheumatoid arthritis, osteoarthritis, multiple sclerosis and psoriasis. Other specifically claimed hydrazine derivatives include the following:



Compound	R1	R2	Formula
272427	i-Bu	SO ₂ Me	C ₂₂ H ₃₅ N ₃ O ₅ S
272428	(S)-CH ₂ CH(Me)Et	SO ₂ Me	C ₂₃ H ₃₇ N ₃ O ₅ S
272429	CH ₂ C(Me)=CH ₂	SO ₂ Me	C ₂₂ H ₃₃ N ₃ O ₅ S
272430	i-Bu	CO ₂ Me	C ₂₃ H ₃₅ N ₃ O ₅

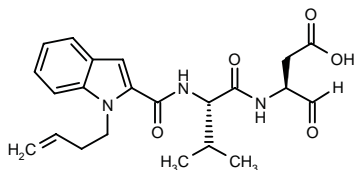
SOURCE – Roche.

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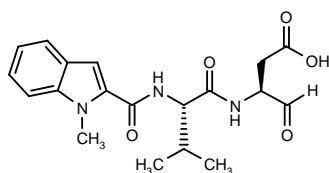
272641

N-[1-(3-Butenyl)-1*H*-indol-2-ylcarbonyl]-L-valyl-L-aspart-1-al



C22 H27 N3 O5; Mol wt: 413.4713

ACTION – Agent for the treatment of inflammatory, autoimmune and neurodegenerative diseases, as well as for the prevention of ischemic injury and the preservation of organs for transplantation, an inhibitor of the IL-1 β -converting enzyme (ICE)/ced-3 family of cysteine proteases. Another exemplified compound from this series of 2-indolyl dipeptides is:



272642: C19 H23 N3 O5

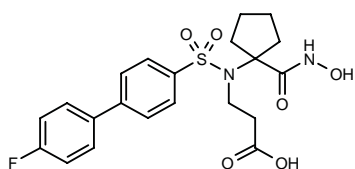
SOURCE – Idun.

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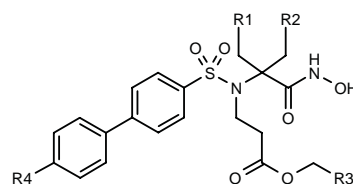
272686

3-[*N*-(4'-Fluorobiphenyl-4-ylsulfonyl)-*N*-[1-(*N*-hydroxycarbonyl)cyclopentyl]amino]propionic acid



C21 H23 F N2 O6 S; Mol wt: 450.4847

ACTION – An inhibitor of matrix metalloproteinases (MMPs) and the production of tumor necrosis factor (TNF) with potential in the treatment of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, bone resorption, atherosclerosis, multiple sclerosis, ocular angiogenesis, AIDS, sepsis and other diseases characterized by MMP activity and/or involving the production of TNF. *In vitro*, compound exhibited selectivity for collagenase 3 (MMP-13) relative to fibroblast collagenase (MMP-1), as demonstrated by IC₅₀ values in the range of 1.7-3.5 and 195-300 nM, respectively. A representative compound from a series of arylsulfonylamino hydroxamic acid derivatives, wherein the following are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
272687	-(CH2)2-		H	H	C ₂₂ H ₂₆ N ₂ O ₆ S
272688	H	H	Me	F	C ₂₁ H ₂₅ FN ₂ O ₆ S

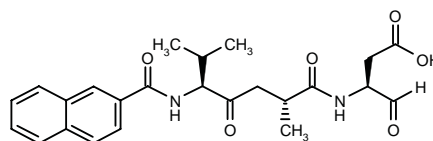
SOURCE – Pfizer.

REFERENCES

1. Robinson, R.P. (Pfizer Products Inc.) *Arylsulfonylamino hydroxamic acid derivs.* EP 895988.

272786

N-[2(*R*)-Methyl-3-[*N*-(2-naphthylcarbonyl)-L-valyl]propion-yl]-L-aspart-1-al



C24 H28 N2 O6; Mol wt: 440.4932

ACTION – Peptide inhibitor of cysteine proteases such as IL-1 β -converting enzyme (ICE), giving an IC₅₀ value of 56 nM against recombinant ICE.

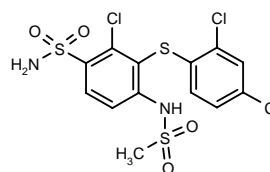
SOURCE – Takeda.

REFERENCES

1. Kamata, M. et al. (Takeda Chemical Industries, Ltd.) *Peptides and their agents.* JP 99001491.

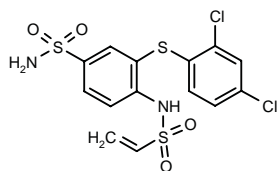
272890

2-Chloro-3-(2,4-dichlorophenylsulfanyl)-4-(methylsulfonylamido)benzenesulfonamide



C13 H11 Cl3 N2 O4 S3; Mol wt: 461.7969

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.10 μ M) with 250-fold selectivity relative to COX-1 (IC₅₀ = 25 μ M) *in vitro*. Another compound from this series of substituted benzenesulfonamides is:



272891: C14 H12 Cl2 N2 O4 S3

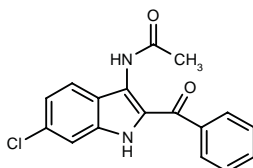
SOURCE – Nycomed Pharma.

REFERENCES

1. Hartmann, M. et al. (Nycomed Austria GmbH) *Substd. derivs. of benzosulphonamides as inhibitors of the enzyme cyclooxygenase II*. WO 9833769.

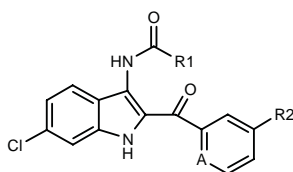
272968

N-(2-Benzoyl-6-chloro-1*H*-indol-3-yl)acetamide



C17 H13 Cl N2 O2; Mol wt: 312.7547

ACTION – Antiinflammatory and analgesic agent with cyclooxygenase type 2 (COX-2)-inhibitory activity. Other specifically claimed compounds within this series of indole derivatives include the following:



Compound	R1	R2	A	Formula
272969	i-Bu	H	CH	C ₂₀ H ₁₉ ClN ₂ O ₂
272970	Me	Me	CH	C ₁₈ H ₁₅ ClN ₂ O ₂
272971	Me	Cl	CH	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂
272972	Et	Cl	CH	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂
272973	Me	Me	N	C ₁₇ H ₁₄ ClN ₃ O ₂
272974	CH ₂ SM	H	CH	C ₁₈ H ₁₅ ClN ₂ O ₂ S
272975	Et	Cl	N	C ₁₇ H ₁₃ Cl ₂ N ₃ O ₂
272976	CH(Me)2OH	Cl	N	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₃

SOURCE – Pfizer.

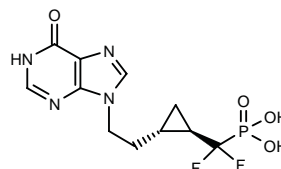
REFERENCES

1. Stevens, R.W. et al. (Pfizer Inc.) *Indole cpds. as COX-2 inhibitors*. WO 9905104.

IMMUNOMODULATING AGENTS

270250

(±)-1,1-(Difluoro)-1-[(1*R**,2*S**)-2-[2-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)ethyl]cyclopropyl]methylphosphonic acid



C11 H13 F2 N4 O4 P; Mol wt: 334.2177

Amorphous powder.

ACTION – Purine nucleoside phosphorylase (PNP) inhibitor with a *K_i* value of 8.8 nM against purified PNP from *Cellulomonas* sp. and of 17.3 nM against enzyme from human erythrocytes. Potentially useful as an immunosuppressant, as well as in the treatment of T-cell proliferative diseases such as T-cell leukemia.

SOURCE – University of Tokyo, Tokyo (JP).

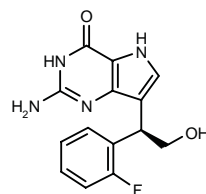
REFERENCES

1. Yokomatsu, T. et al. *Synthesis of 1,1-difluoro-5-(1*H*-9-purinyll)-2-pentenylphosphonic acids and the related methano analogues. Remarkable effect of the nucleobases and the cyclopropane rings on inhibitory activity toward purine nucleoside phosphorylase*. Bioorg Med Chem 1998, 6(12): 2495.

2. Yokomatsu, T. et al. *Synthesis of novel nucleotide analogues possessing difluoromethylene phosphonate pharmacophore. Evaluation of the inhibitory activities of PNPases*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-06.

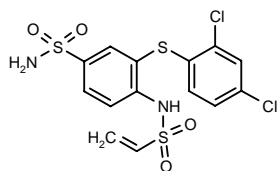
271880

2-Amino-7-[1(*R*)-(2-fluorophenyl)-2-hydroxyethyl]-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidin-4-one



C14 H13 F N4 O2; Mol wt: 288.2807

ACTION – Purine nucleoside phosphorylase (PNP) inhibitor useful for selectively suppressing T-cell-mediated immunity, with potential in the treatment of autoimmune diseases, psoriasis and transplant rejection. Compound is also reported to be useful for inhibiting the phosphorolysis and metabolic breakdown of antiviral and antitumor purine nucleosides, as well as for potentiating the antiviral and antitumor effect of 2'- or 3'-monodeoxypurine nucleosides or of 2',3'-dideoxypurine nucleosides. A representative compound from a series of 2-amino-7-(1-substituted-2-hydroxyethyl)-3,5-dihydropyrrolo[3,2-*d*]pyrimidin-4-ones, wherein the following are also included:



272891: C₁₄ H₁₂ Cl₂ N₂ O₄ S₃

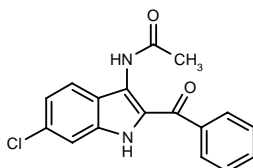
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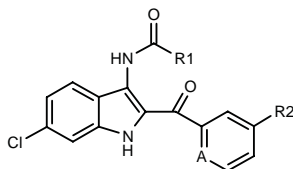
272968

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C₁₇ H₁₃ Cl N₂ O₂; Mol wt: 312.7547

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272971	Me	Cl	CH	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂
272972	Et	Cl	CH	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂
272973	Me	Me	N	C ₁₇ H ₁₄ ClN ₃ O ₂
272974	CH ₂ SMc	H	CH	C ₁₈ H ₁₅ ClN ₂ O ₂ S
272975	Et	Cl	N	C ₁₇ H ₁₃ Cl ₂ N ₃ O ₂
272976	CH(Me)2OH	Cl	N	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₃

SOURCE – Pfizer.

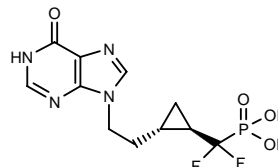
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IMMUNOMODULATING AGENTS

270250

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C₁₁ H₁₃ F₂ N₄ O₄ P; Mol wt: 334.2177

Amorphous powder.

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SOURCE – University of Tokyo, Tokyo (JP).

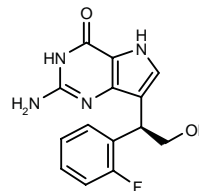
REFERENCES

1. Yokomatsu, T. et al. *Synthesis of 1,1-difluoro-5-(1*H*-9-purinyll)-2-pentenylphosphonic acids and the related methano analogues. Remarkable effect of the nucleobases and the cyclopropane rings on inhibitory activity toward purine nucleoside phosphorylase*. Bioorg Med Chem 1998, 6(12): 2495.

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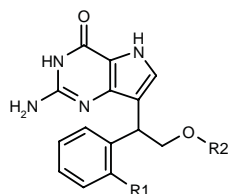
271880

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C₁₄ H₁₃ F N₄ O₂; Mol wt: 288.2807

ACTION – Purine nucleoside phosphorylase (PNP) inhibitor useful for selectively suppressing T-cell-mediated immunity, with potential in the treatment of autoimmune diseases, psoriasis and transplant rejection. Compound is also reported to be useful for inhibiting the phosphorolysis and metabolic breakdown of antiviral and antitumor purine nucleosides, as well as for potentiating the antiviral and antitumor effect of 2'- or 3'-monodeoxypurine nucleosides or of 2',3'-dideoxypurine nucleosides. A representative compound from a series of 2-amino-7-(1-substituted-2-hydroxyethyl)-3,5-dihydropyrrolo[3,2-*d*]pyrimidin-4-ones, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
271881	H	H		C ₁₄ H ₁₄ N ₄ O ₂
271892	F	COC(Me)2OMe	R	C ₁₉ H ₂₁ N ₄ O ₄
271893	OMe	H		C ₁₅ H ₁₆ N ₄ O ₃

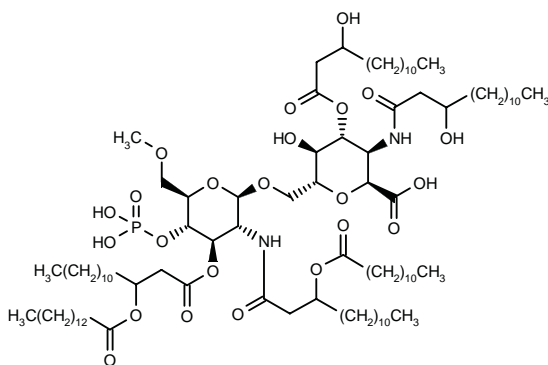
SOURCE – Novartis.

REFERENCES

1. Van Duzer, J.H. et al. (Novartis AG) *2-Amino-7-(1-substd.-2-hydroxyethyl)-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-ones*. WO 9854185.

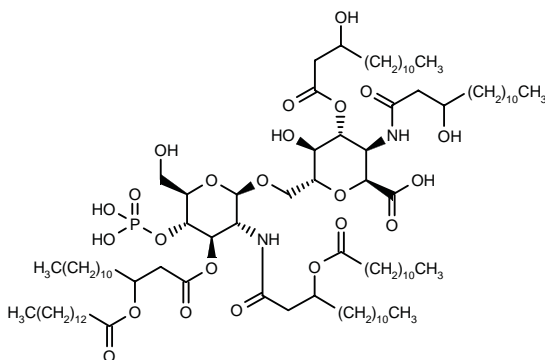
272111

2-Deoxy-6-*O*-[2-deoxy-2-[3-(dodecanoyloxy)-tetradecanamido]-6-*O*-methyl-4-*O*-phosphono-3-*O*-[3-(tetradecanoyloxy)tetradecanoyl]-β-D-glucopyranosyl]-2-(3-hydroxytetradecanamido)-3-*O*-(3-hydroxytetradecanoyl)-D-glucopyranos-1α-ylcarboxylic acid



C96 H179 N2 O23 P; Mol wt: 1760.4350

ACTION – Immunostimulant and antineoplastic agent with macrophage-activating effects, as demonstrated by the ability to stimulate the production of tumor necrosis factor (TNF-α) in human monocytes. Another representative compound within this series of lipid A derivatives is:



272112: C95 H177 N2 O23 P

Some compounds within the scope of the invention are reported to possess potent macrophage-inhibitory effects and are thus potentially useful for the treatment of inflammatory disorders, autoimmune diseases and septicemia.

SOURCE – Sankyo.

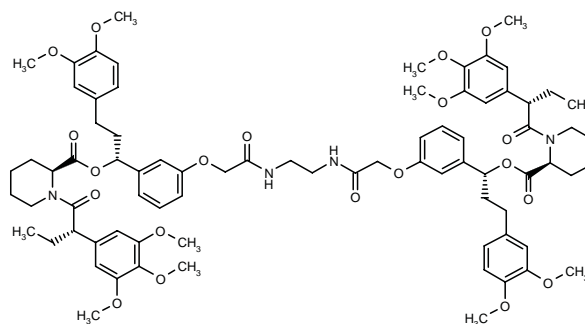
REFERENCES

1. Mochizuki, T. et al. (Sankyo Co., Ltd.) *Lipid A derivs. having carboxylic acid on the 1-position*. JP 98324694.

AP-1903

270609

Bis[1-[2(*S*)-(3,4,5-Trimethoxyphenyl)butyryl]piperidine-2(*S*)-carboxylic acid] ester with 1,2-ethanediylbis[imino(2-oxo-2,1-ethanediyl)oxy-3,1-phenylene[(1*R*)-3-(3,4-dimethoxyphenyl)propylidene]]



C78 H98 N4 O20; Mol wt: 1411.6400

ACTION – Small-molecule dimerizer drug designed to be used as a component of the ARGENT(TM) (Ariad Regulated Gene Expression Technology) graft-versus-host disease (GVHD) product to activate the apoptosis protein in genetically modified donor T-cells, inducing selective cell elimination. This therapy consists of harvesting T-cells from donor peripheral blood prior to the bone marrow graft, isolating and genetically engineering these cells to include a gene for an inactive apoptosis protein; the engineered T-cells are infused into the patient along with bone marrow graft and AP-1903 is administered if the patient exhibits a GVH response. It was found to bind with high affinity and specificity to a mutated FKBP (F36V-FKBP; IC₅₀ = 5 nM) relative to the wild-type protein (1000-fold selectivity). In human fibrosarcoma HT1080 cells expressing the mutated F36V-FKBP protein, compound induced apoptotic cell death with an IC₅₀ value of about 0.1 nM and this activity was reduced approximately 2 orders of magnitude in cells expressing wild-type FKBP. Currently undergoing phase I trials as a treatment for GVHD in patients undergoing allogeneic bone marrow or hematopoietic stem cell transplants.

SOURCE – Ariad.

REFERENCES

1. Holt, D.A. et al. (Ariad Gene Therapeutics, Inc.) *Synthetic derivs. of rapamycin as multimerizing agents for chimeric proteins with immunophilin-derived domains*. WO 9731898.
2. Clackson, T. et al. *Redesigning an FKBP-ligand interface to generate chemical dimerizers with novel specificity*. Proc Natl Acad Sci USA 1998, 95(18): 10437.

3. *Ariad initiates phase I trial with AP-1903 for treatment of GVHD.* DailyDrugNews.com (Daily Essentials) 1998, Dec 11.

4. *Ariad updates stockholders.* DailyDrugNews.com (Daily Essentials) 1998, Sept 9.

FLUMIST™

271581

Intranasal live attenuated, cold-adapted, trivalent influenza vaccine

ACTION – Trivalent intranasal influenza vaccine under development for the prevention of influenza and associated complications. In a multicenter, double-blind, placebo-controlled phase III study in children, the vaccine was found to be effective as both single- and double-dose regimens (89 and 94% efficacy, respectively) and against both strains of influenza circulating in 1996-1997: A(H3N2) and B. FluMist™ also showed good protection against febrile otitis media, a common complication of influenza in children.

SOURCES – Aviron; licensed to CSL and Wyeth-Ayerst; manufactured by Medeva.

REFERENCES

1. Belshe, R. et al. *Efficacy of a trivalent live attenuated intranasal influenza vaccine in children.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst S-116.

2. Belshe, R.B. et al. *The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children.* New Engl J Med 1998, 338(20): 1405.

3. *Aviron and CSL enter collaboration for FluMist.* DailyDrugNews.com (Daily Essentials) 1998, June 26.

4. *Aviron's FluMist influenza vaccine is effective in children.* DailyDrugNews.com (Daily Essentials) 1998, May 15.

5. *Aviron's FluMist PLA/ELA deemed nonfilable by FDA; resubmission planned.* DailyDrugNews.com (Daily Essentials) 1998, Sept 15.

6. *Aviron: Q2 and HY fiscal 1998 highlights.* DailyDrugNews.com (Daily Essentials) 1998, Sept 8.

7. *Collaboration between Wyeth and Aviron for FluMist effective immediately.* DailyDrugNews.com (Daily Essentials) 1999, March 23.

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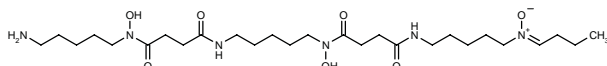
9. *Global FluMist collaboration announced by Aviron and Wyeth Lederle Vaccines.* DailyDrugNews.com (Daily Essentials) 1999, Jan 14.

10. *Status of FluMist influenza vaccine updated by Aviron.* DailyDrugNews.com (Daily Essentials) 1998, Dec 11.

IC-202A

271861

(Z)-32-Amino-16,27-dihydroxy-12,15,23,26-tetraoxo-11,16,22,27-tetraaza-5-azonia-4-dotriaconten-5-olate



C27 H52 N6 O7; Mol wt: 572.7428

ACTION – Immunosuppressant siderophore isolated from the culture broth of *Streptoalloteichus* sp. 1454-19, with suppressive effect on the murine mixed lymphocyte

reaction (MLR; IC₅₀ = 3.6 µg/ml). Compound also exhibited suppressive effects on mitogen (concanavalin A and lipopolysaccharide)-induced lymphocyte blastogenesis (IC₅₀ = 9.6 and 11.3 µg/ml, respectively) and was cytotoxic against several tumor cell lines such as leukemia P388, LB32T and HL60 cells (IC₅₀ = 7-20 µg/ml), although at concentrations higher than those required to inhibit the MLR.

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Iijima, M. et al. *IC202A, a new siderophore with immunosuppressive activity produced by Streptoalloteichus sp. 1454-19. I. Taxonomy, fermentation, isolation and biological activity.* J Antibiot 1999, 52(1): 20.

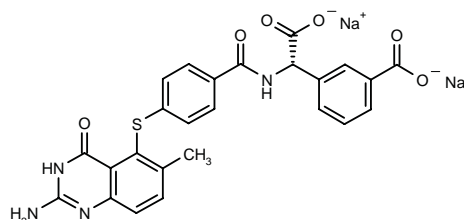
2. Iijima, M. et al. *IC202A, a new siderophore with immunosuppressive activity produced by Streptoalloteichus sp. 1454-19. II. Physico-chemical properties and structure elucidation.* J Antibiot 1999, 52(1): 25.

ONCOLYTIC DRUGS

ANTIMETABOLITES

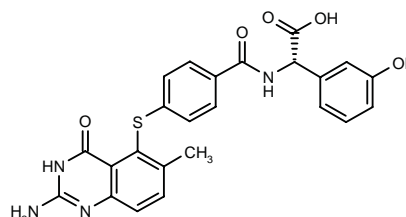
270681

2(S)-[4-(2-Amino-6-methyl-4-oxo-3,4-dihydroquinazolin-5-ylsulfanyl)benzamido]-2-(3-carboxyphenyl)acetic acid disodium salt



C25 H18 N4 O6 S . 2 Na; Mol wt: 548.4852

ACTION – Antineoplastic agent that acts by inhibiting thymidylate synthase and was found to inhibit the growth of tumor cell lines such as murine lymphocytic leukemia L1210, murine thymidine kinase-deficient lymphoma LY3.7.2C TK^{-/-}, human leukemia CCRF-CEM and human colon adenocarcinoma HT-29 cells with IC₅₀ values of 0.5, 0.7, 0.05 and 1.2 µM, respectively. It has been reported to induce cures in BDF1 mice bearing LY3.7.2C TK^{-/-} cells when administered as the disodium salt twice daily at a dose of 120 mg/kg i.p. for 10 days. Another related compound is:



270679: C24 H20 N4 O5 S

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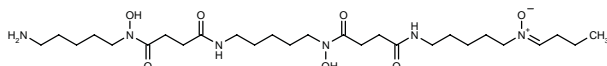
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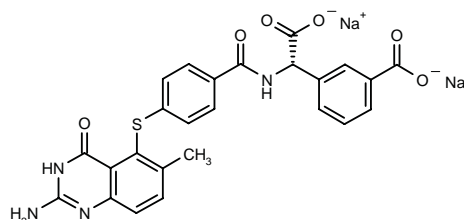
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ONCOLYTIC DRUGS

ANTIMETABOLITES

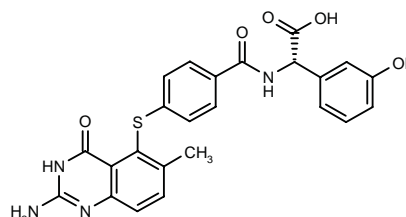
270681

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270679: C24 H20 N4 O5 S

SOURCE – Choongwae.

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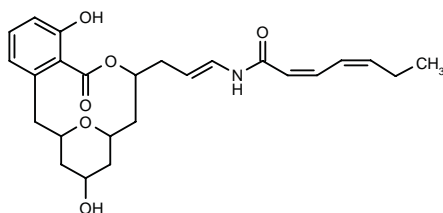
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ANTIBIOTICS AND ALKALOIDS

APICULAREN A

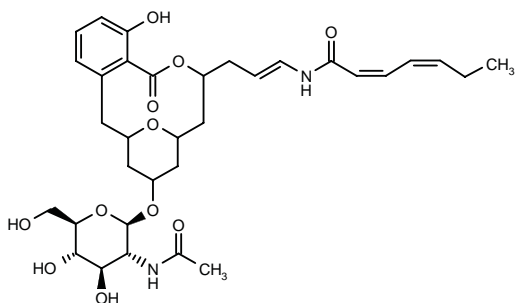
271156

N-[3-(5,9-Epoxy-7,14-dihydroxy-1-oxo-3,4,5,6,7,8,9,10-octahydro-1*H*-2-benzoxecin-3-yl)-1(*E*)-propenyl]-2(*Z*),4(*Z*)-heptadienamide



C25 H31 N O6; Mol wt: 441.5209

ACTION – Potent cytostatic macrolide produced by several species of *Chondromyces*, with excellent cytostatic activity against various human tumor cell lines such as cervical, kidney, lung, prostate and ovarian carcinoma (IC_{50} = 0.1-1.5 ng/ml), as well as against chronic myelogenous and acute myeloid leukemia (IC_{50} = 2 and 3 ng/ml, respectively). Compound was completely inactive against both Gram-positive and Gram-negative bacteria, as well as against yeasts and fungi. Another related macrolide is:



Apicularen B [271157]: C33 H44 N2 O11

SOURCE – GBF.

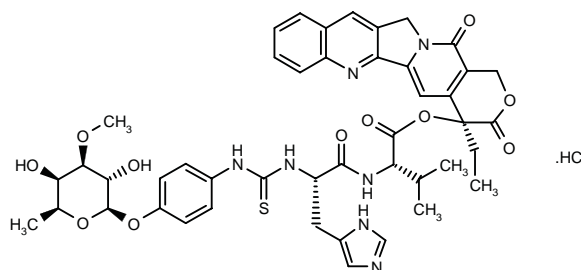
REFERENCES

1. Kunze, B. et al. *Apicularens A and B, new cytostatic macrolides from Chondromyces species (myxobacteria): Production, physico-chemical and biological properties*. *J Antibiot* 1998, 51(12): 1075.

DNA-INTERCALATING DRUGS

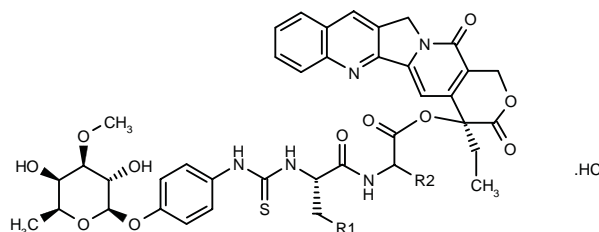
271380

N-[4-(6-Deoxy-3-*O*-methyl- β -L-galactopyranosyloxy)-phenylaminothiocarbonyl]-L-histidyl-L-valine 4(*S*)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]-indolizino[1,2-*b*]quinolin-4-yl ester hydrochloride



C45 H49 N7 O11 S . Cl H; Mol wt: 932.4470

ACTION – Antineoplastic agent, a camptothecin glycoconjugate proven active *in vitro* with IC_{50} values of 200, 70 and 400 nM, respectively, against human tumor SW480 and HT29 and mouse melanoma B16F10 cells (IC_{50} 20(*S*)-camptothecin = 10, 5 and 20 nM, respectively). Compound also inhibited granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced proliferation of mouse bone marrow cells (IC_{50} = 15 ng/ml). Other exemplified camptothecin glycoconjugates are:



Compound	R1	R2	Formula
271381	(CH2)3NH2	i-Bu	C ₄₈ H ₅₈ N ₆ O ₁₁ S.HCl
271382	(CH2)3NH2	(S)-i-Pr	C ₄₈ H ₅₄ N ₆ O ₁₁ S.HCl
271383	5-imidazolyl	i-Pr	C ₄₅ H ₄₉ N ₇ O ₁₁ S.HCl

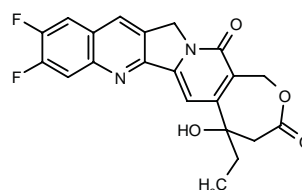
SOURCE – Bayer.

REFERENCES

1. Lerchen, H.-G. et al. (Bayer AG) 20(*S*) Camptothecin glycoconjugates. WO 9851703.

271570

5-Ethyl-9,10-difluoro-5-hydroxy-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione



C21 H16 F2 N2 O4; Mol wt: 398.3634

Off-white solid, *m.p.* > 250 °C.

ACTION – Antineoplastic agent, a camptothecin (CPT) analogue with potent cytotoxic activity against human tumor cell lines such as human lung carcinoma A427 and human prostate adenocarcinoma PC-3 (IC_{50} = 0.1 and 0.0010 nM, respectively), as well as doxorubicin-resistant leukemia K562*adr* cells (IC_{50} = 66 nM). Compound acts via a mechanism involving inhibition of topoisomerase I and was at least as active as CPT in antagonizing topo I-mediated DNA relaxation (about 40% inhibition at 100 μ M). *In vivo* in athymic mice bearing established human colon adenocarcinoma HT-29 xenografts, compound given i.p. at a dose of 0.32 mg/kg/day induced tumor growth delay of 25 days and tumor regression, exhibiting higher efficacy than CPT (tumor growth delay of 4 days at a dose of 0.625 mg/kg/day i.p.). It showed improved stability in human plasma compared to CPT. A promising candidate for development, its enantiopure form is undergoing preclinical evaluation.

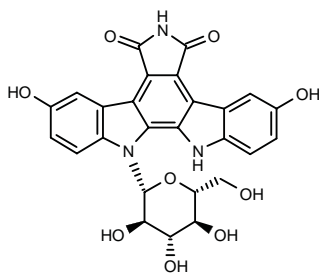
SOURCES – Beaufour-Ipsen; Biomeasure; Lasa.

REFERENCES

1. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel camptothecin analogues, preparation methods therefor, use thereof as drugs, and pharmaceutical compns. containing said analogues*. EP 835258, WO 9700876.
2. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel counterparts of camptothecin, their application as medicine and pharmaceutical compns. containing them*. FR 2757514, WO 9828305.
3. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Pro-drugs and counterparts of camptothecin, their application as medicines*. WO 9828304.
4. Lavergne, O. et al. *Homocamptothecins: Synthesis and antitumor activity of novel E-ring-modified camptothecin analogues*. J Med Chem 1998, 41(27): 5410.

271996

12-(β -D-Glucopyranosyl)-3,9-dihydroxy-6,7,12,13-tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C26 H21 N3 O9; Mol wt: 519.4639

ACTION – Antineoplastic agent, an inhibitor of topoisomerase I (topo I) with improved activity relative to the parent compound ED-110 (IC_{50} = 1.5 and 13 μ M, respectively, against human topo I). Compound exhibited a broad spectrum of cytotoxicity against colon cancer HT-29, ovarian cancer OVCAR-3 and prostate cancer DU-145 cells (IC_{50} = 0.84, 0.19 and 0.067 μ M, respectively), being 5-30-fold more active than ED-110.

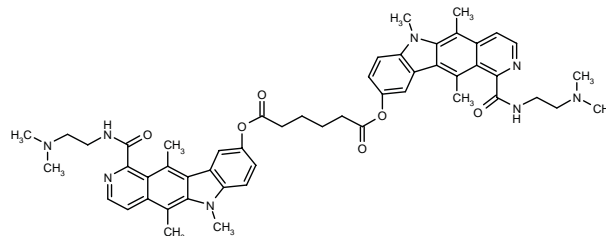
SOURCE – MediChem.

REFERENCES

1. Zembower, D.E. et al. *Indolocarbazole poisons of human topoisomerase I: Regioisomeric analogues of ED-110*. Bioorg Med Chem Lett 1999, 9(2): 145.

272682

Adipic acid bis[1-[2-(*N,N*-dimethylamino)ethyl]carbamoyl]-5,6,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazol-9-yl] diester



C52 H58 N8 O6; Mol wt: 891.0802

ACTION – Antineoplastic agent with potent cytotoxicity against murine L1210 leukemia, murine melanoma B16 and human pulmonary carcinoma A549 cells (IC_{50} = 73.5, 3.0 and 17.6 nM, respectively; IC_{50} doxorubicin = 24.3, 6.8 and 39.4 nM, respectively). *In vivo*, it increased survival time of mice bearing P388 leukemia, with T/C x 100 values of 252 and > 582%, respectively, when given at 10 mg/kg i.v. on day 1 and 10 mg/kg i.v. on days 1, 5 and 9. Antitumor activity was also shown in mice bearing B16 melanoma (T/C x 100 = 429% at 5 mg/kg/day i.v. x 9 days). A representative compound from a series of ellipticine and olivacine derivatives.

SOURCE – ADIR.

REFERENCES

1. Guillonnet, C. et al. (ADIR et Cie.) *Bis pyrido[4,3-*b*]carbazole cpds., process for their preparation and pharmaceutical compns. containing them*. EP 895995.

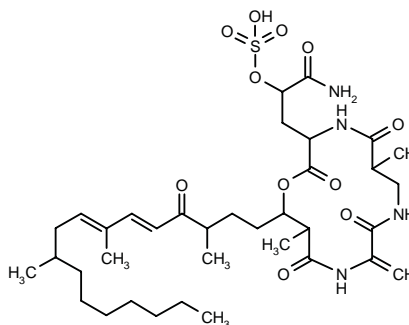
TOPOSTATIN

270406

3-[2-Carbamoyl-2-(sulfooxy)ethyl]-6,13-dimethyl-10-methylene-14-[3,7,10-trimethyl-4-oxoheptadeca-5(*E*),7(*E*)-dienyl]-1-oxa-4,8,11-triazacyclotetradecane-2,5,9,12-tetraone

2-[2-Carbamoyl-2-(sulfooxy)ethyl]-5,12,16,20,23-pentamethyl-9-methylene-4,8,11,17-tetraoxo-3,7,10-triazatriaconta-18(*E*),20(*E*)-dieno-13-lactone

3-[6,13-Dimethyl-10-methylene-14-[3,7,10-trimethyl-4-oxoheptadeca-5(*E*),7(*E*)-dienyl]-2,5,9,12-tetraoxo-1-oxa-4,8,11-triazacyclotetradecan-3-yl]-2-(sulfooxy)-propionamide



C36 H58 N4 O11 S; Mol wt: 754.9372

Yellowish white powder, m.p. 179-86 °C (decomp.), $[\alpha]_D^{28}$ +18.3° (c 0.1, MeOH).

ACTION – Antineoplastic agent, an inhibitor of topoisomerase I and II (IC_{50} = 13 and 3 ng/ μ l, respectively) isolated from a culture filtrate of *Thermomonospora alba* strain no. 1520. Compound did not intercalate into DNA strands at up to 30 ng/ μ l and it did not stabilize cleavable complexes of topoisomerase I and II at up to 1 μ g/ml. Topostatin exhibited strong cytostatic activity against the two human CNS tumor cell lines SNB-75 and SNB-78 (IC_{50} = 0.4 and 7 μ M, respectively) and weak growth inhibition against breast cancer BSY-1 and MDA-MB-231 cells (IC_{50} = 59 and 64 μ M, respectively) and other types of tumor cells. Compound did not exhibit significant antimicrobial activity against Gram-positive and Gram-negative bacteria, yeast or fungi at up to 100 μ g/ml.

SOURCE – Kumamoto University, Kumamoto (JP).

REFERENCES

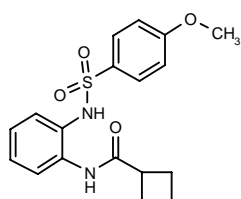
1. Suzuki, K. et al. *Topostatin, a novel inhibitor of topoisomerases I and II produced by Thermomonospora alba strain No. 1520. I. Taxonomy, fermentation, isolation and biological activities.* J Antibiot 1998, 51(11): 991.

2. Suzuki, K. et al. *Topostatin, a novel inhibitor of topoisomerases I and II produced by Thermomonospora alba strain No. 1520. II. Physico-chemical properties and structure elucidation.* J Antibiot 1998, 51(11): 999.

ANTIMITOTIC DRUGS

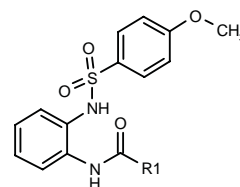
272155

N-[2-(4-Methoxyphenylsulfonamido)phenyl]cyclobutanecarboxamide



C₁₈ H₂₀ N₂ O₄ S; Mol wt: 360.4320

ACTION – Antineoplastic agent with low toxicity, also useful for the treatment of rheumatoid arthritis. It inhibits tubulin polymerization (IC_{50} = 1.15 μ g/ml using porcine brain-derived microtubular protein) and it displayed *in vitro* cytotoxicity against human ovarian cancer A2780 cells (IC_{50} = 0.006 μ g/ml). Also reported to prevent the development of collagen-induced arthritis in mice. Within this series of sulfonamide derivatives, the following are also included:



Compound	R1	Formula
272156	5-Me-4-isoxazolyl	C ₁₈ H ₁₇ N ₃ O ₅ S
272157	3,5-(Me)2-4-isoxazolyl	C ₁₉ H ₁₉ N ₃ O ₅ S
272158	5-Et-4-isoxazolyl	C ₁₉ H ₁₉ N ₃ O ₅ S
272159	cyclohexyl	C ₂₀ H ₂₄ N ₂ O ₄ S
272160	cyclopropyl	C ₁₇ H ₁₈ N ₂ O ₄ S
272161	cyclopentyl	C ₁₉ H ₂₂ N ₂ O ₄ S
272162	3-Et-5-Me-4-isoxazolyl	C ₂₀ H ₂₁ N ₃ O ₅ S
272163	5-Et-3-Me-4-isoxazolyl	C ₂₀ H ₂₁ N ₃ O ₅ S

SOURCE – Nippon Kayaku.

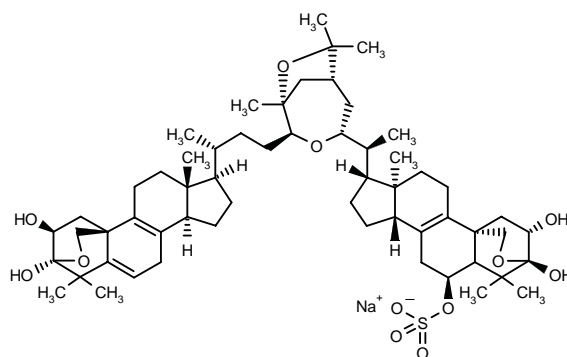
REFERENCES

1. Morohashi, H. and Sato, H. (Nippon Kayaku Co., Ltd.) *Novel sulfonamide derivs.* WO 9854131.

CRELLASTATIN A

271675

3,19-Epoxy-20(*S*)-[2-[[1*R*,2*S*(2 β ,3 β)4*R*,6*R*]-3,19-epoxy-2,3-dihydroxy-4,4-dimethyl-24-norchola-5,8-dien-23-yl]-1,7,7-trimethyl-3,8-dioxabicyclo[4.2.1]non-4-yl]-4,4-dimethyl-6 α -(sulfooxy)pregn-8-ene-2 β ,3 β -diol monosodium salt



C₅₈ H₈₇ Na O₁₂ S; Mol wt: 1031.3690

Amorphous solid, [α]_D +55° (*c* 1, MeOH).

ACTION – Cytotoxic agent, a nonsymmetric dimeric steroid isolated from the Vanuatu Island marine sponge *Crella* sp., with *in vitro* cytotoxicity against human cancer NSCLC-N6 cells (IC_{50} = 1.5 μ g/ml). Compound induced accumulation of cells in the G1 phase of the cell cycle, with subsequent decrease of cells in the S and G2M phases.

SOURCES – University of Nantes, Nantes (FR); Università degli Studi di Napoli, Napoli (IT).

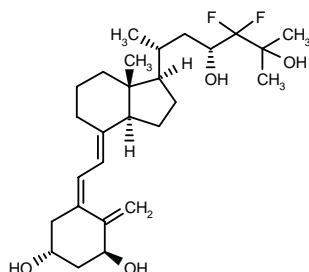
REFERENCES

1. D'Auria, M.V. et al. *Crellastatin A: A cytotoxic bis-steroid sulfate from the vanuatu marine sponge Crella sp.* J Org Chem 1998, 63(21): 7382.

HORMONAL AGENTS

271151^{1,2}

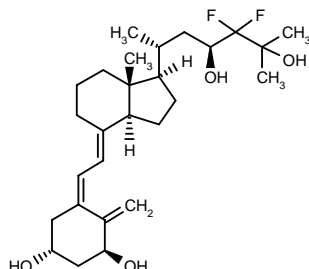
(1 α ,3, β ,5Z,7E,23R)-24,24-Difluoro-9,10-secocholesta-5,7,10(19)-triene-1,3,23,25-tetraol



C27 H42 F2 O4; Mol wt: 468.6208

Colorless oil, $[\alpha]_D^{20} +16.0^\circ$ (c 0.25, EtOH).

ACTION – 1 α ,25-Dihydroxyvitamin D₃ analogue with affinity for the vitamin D receptor (calf thymus) and serum vitamin D-binding protein (DBP; rat) 10- and 130-fold lower, respectively, than the parent compound, but differentiating activity in human leukemia HL-60 cells 6 times higher than 1 α ,25-dihydroxyvitamin D₃. Further biological studies *in vivo* are in progress. Potentially useful as a nonhypercalcemic antitumor and/or antipsoriatic agent. Another related vitamin D analogue is:



271152²: C27 H42 F2 O4

SOURCE – NOF.

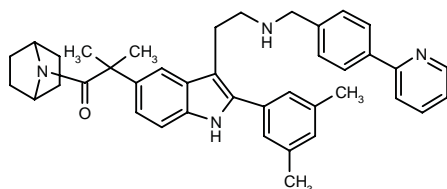
REFERENCES

1. Iwasaki, H. et al. (NOF Corp.) *Vitamin D derivs. and their preparation method*. JP 96239360.

2. Iwasaki, H. et al. *Synthesis and biological evaluation of (23R)- and (23S)-24,24-difluoro-1 α ,23,25-trihydroxyvitamin D₃*. Chem Pharm Bull 1998, 46(12): 1932.

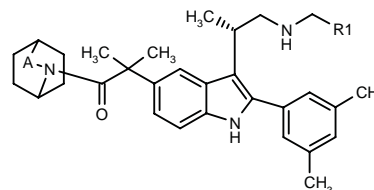
272092

1-(7-Azabicyclo[2.2.1]hept-7-yl)-2-[2-(3,5-dimethylphenyl)-3-[2-[4-(2-pyridinyl)benzylamino]ethyl]-1H-indol-5-yl]-2-methyl-1-propanone

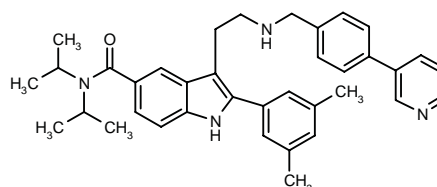


C40 H44 N4 O; Mol wt: 596.8146

ACTION – Nonpeptide antagonist of gonadotropin-releasing hormone (GnRH), as demonstrated in *in vitro* binding assays using human and rat pituitary GnRH receptors. Claimed for use in the treatment of sex hormone-related conditions including uterine and breast cancer, endometriosis and precocious puberty. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	A	Formula
272093	4-(3-Pyr)-Ph	bond	C ₄₁ H ₄₆ N ₄ O
272094	4-(3-Me-1,2,4-oxadiazol-5-yl)-PhCH2	CH2	C ₄₁ H ₄₉ N ₅ O ₂



272095: C37 H42 N4 O

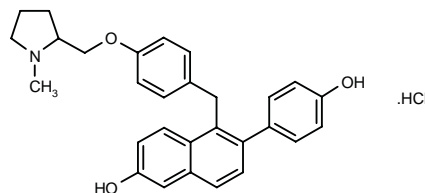
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9855119.

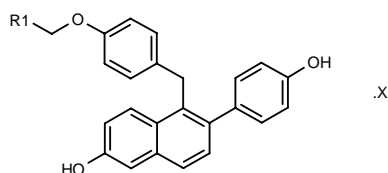
272643

6-[(4-Hydroxyphenyl)-5-[4-(1-methyl-2-pyrrolidinyl)-methoxybenzyl]-2-naphthalenol hydrochloride



C29 H29 N O3 . HCl; Mol wt: 476.0130

ACTION – Selective estrogen receptor modulator (SERM) with potential in the treatment of estrogen-related disorders, particularly breast and uterine cancer. Within this series of 1-(4-alkoxybenzyl)naphthalene derivatives, the following are also included:



Compound	R1	X	Formula
272646	CH ₂ CH ₂ N(Et) ₂	HCl	C ₃₀ H ₃₃ NO ₃ ·HCl
272647	CH ₂ N(i-Pr) ₂	HCl	C ₃₁ H ₃₅ NO ₃ ·HCl
272648	1-Me-2-Pip	HCl	C ₃₀ H ₃₁ NO ₃ ·HCl
272649	1-Me-3-Pip	HCl	C ₃₀ H ₃₁ NO ₃ ·HCl
272650	CH ₂ N(Bu) ₂	HCl	C ₃₃ H ₃₉ NO ₃ ·HCl
272651	CH ₂ CH ₂ N(Bu) ₂	HCl	C ₃₄ H ₄₁ NO ₃ ·HCl
272652	4-(4-Ac-Ph)-1-Piz-CH ₂	2HCl	C ₃₇ H ₃₆ N ₂ O ₄ ·2HCl
272653	1-Naph-NHCH ₂ CH ₂	HCl	C ₃₆ H ₃₁ NO ₃ ·HCl
272654	(CH ₂) ₅ N(Pr) ₂	HCl	C ₃₅ H ₄₃ NO ₃ ·HCl
272655	5-Cl-2-Me-PhNHCON(Et)CH ₂		C ₃₅ H ₃₃ ClN ₂ O ₄
272656	1,3-(Me)2-8-xanthinyl	HCl	C ₃₂ H ₃₀ N ₄ O ₅ ·HCl
272657	2,6-(Me)2-4-morpholinyl-CH ₂	HCl	C ₃₁ H ₃₃ NO ₄ ·HCl
272658	4-azaspiro[5.5]undec-4-yl-CH ₂ CH ₂	HCl	C ₃₆ H ₄₁ NO ₃ ·HCl
272659	2-oxo-1-pyrrolidinyl-CH ₂		C ₂₉ H ₂₇ NO ₄
272660	2-oxo-1-pyrrolidinyl-CH ₂ CH ₂		C ₃₀ H ₂₉ NO ₄

SOURCE – Lilly.

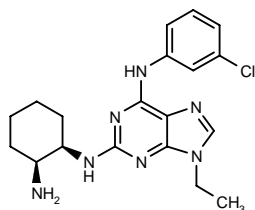
REFERENCES

- Dodge, J.A. et al. (Eli Lilly and Company) 1-[4-(Subst. alkoxy)benzyl] naphthalene cpds. having estrogen inhibitory activity. EP 895989, WO 9907377.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

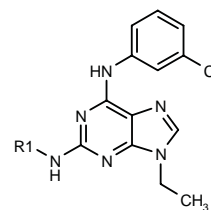
271394

*N*²-(*cis*-2-Aminocyclohexyl)-*N*⁶-(3-chlorophenyl)-9-ethyl-9*H*-purine-2,6-diamine



C₁₉ H₂₄ Cl N₇; Mol wt: 385.9006

ACTION – Antineoplastic agent, a potent cyclin-dependent type 1 kinase (CDK1) inhibitor (IC₅₀ = 24 nM) with high selectivity over other kinases such as protein kinase C-α (PKC-α), protein kinase A (PKA) and epidermal growth factor (EGF) protein kinase (IC₅₀ = 6.1, 125 and > 10 μM, respectively). Compound displayed antiproliferative activity against human bladder carcinoma T24 cells, giving an IC₅₀ of 0.48 μM. Other compounds from this series of 2,6,9-trisubstituted purines are:



Compound	R1	Formula
271393	trans-4-OH-cyclohexyl	C ₁₉ H ₂₃ ClN ₆ O
271395	trans-4-NH ₂ -cyclohexyl	C ₁₉ H ₂₄ ClN ₇
271396	CH ₂ CH ₂ NH ₂	C ₁₅ H ₁₈ ClN ₇

SOURCE – Novartis.

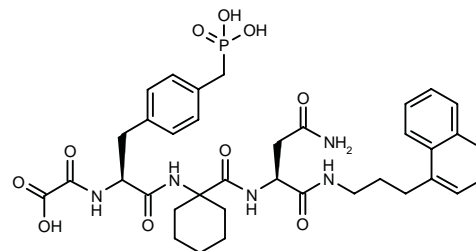
REFERENCES

- Zimmermann, J. et al. (Novartis AG) Purine derivs. and processes for their preparation. WO 9716452.

- Imbach, P. et al. 2,6,9-Trisubstituted purines: Optimization towards highly potent and selective CDK1 inhibitors. Bioorg Med Chem Lett 1999, 9(1): 91.

272048

N-(2-Hydroxy-1,2-dioxoethyl)-4-(phosphonomethyl)-L-phenylalanyl-(1-aminocyclohexylcarbonyl)-L-asparagine 3-(1-naphthyl)propylamide



C₃₆ H₄₄ N₅ O₁₀ P; Mol wt: 737.7426

ACTION – Potential antineoplastic agent that acts as a growth factor receptor-bound protein 2 (Grb2) SH2 domain blocker. Compound inhibited the interaction between native Grb2 and a phosphorylated gene product, p185^{erbB-2}, both in a whole-cell assay in human breast cancer-derived MDA-MB-453 cells (IC₅₀ = 0.5 μM) and in cell lysates.

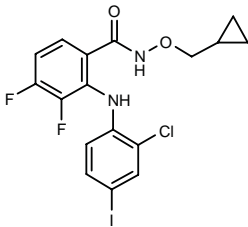
SOURCES – Georgetown University, Washington, DC (US); National Cancer Institute, Bethesda, MD (US).

REFERENCES

- Yao, Z.-J. et al. Potent inhibition of Grb2 SH2 domain binding by non-phosphate-containing ligands. J Med Chem 1999, 42(1): 25.

272343

2-(2-Chloro-4-iodophenylamino)-N-(cyclopropylmethoxy)-3,4-difluorobenzamide



C17 H14 Cl F2 I N2 O2; Mol wt: 478.6586

ACTION – Antineoplastic and antiproliferative agent, a potent and selective inhibitor of the protein kinases MEK1 and MEK2. Compound was assessed *in vivo* for its ability to inhibit tumor growth in mice bearing murine colon tumor C26/clone 10, where it produced 59-100% inhibition at 48-200 mg/kg/day i.p. and 64-83% inhibition at oral doses of 71-300 mg/kg/day.

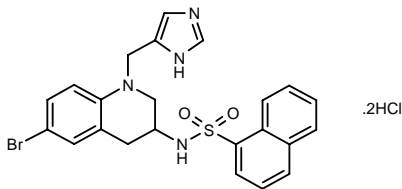
SOURCE – Warner-Lambert.

REFERENCES

1. Barrett, S.D. et al. (Warner-Lambert Co.) *4-Bromo or 4-iodo phenylamino benzhydroxamic acid derivs. and their use as MEK inhibitors.* WO 9901426.

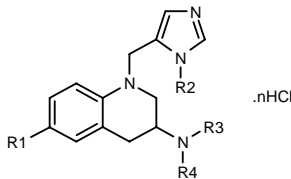
272384

N-[6-Bromo-1-(1*H*-imidazol-5-ylmethyl)-1,2,3,4-tetrahydro-3-quinolinyl]-1-naphthalenesulfonamide dihydrochloride

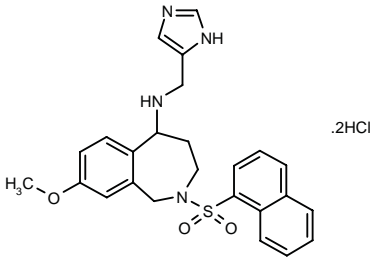


C23 H21 Br N4 O2 S . 2 HCl; Mol wt: 570.3367

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogenic protein Ras. Within this series of specifically claimed quinoline and benzazepine derivatives, the following are also included:



Compound	R1	R2	R3	R1	n	Isomer	Formula
272385	Br	H	1-Naph-CO	H	2		C ₂₄ H ₂₁ BrN ₄ O .2HCl
272386	Br	H	CH ₂ Ph	SO ₂ Me	2		C ₂₁ H ₂₃ BrN ₄ O ₂ S .2HCl
272388	Br	H	4-MeO-PhCH ₂	SO ₂ Me	1		C ₂₂ H ₂₆ BrN ₄ O ₃ S .HCl
272390	CN	Me	CH ₂ Ph	SO ₂ Ph	1		C ₂₈ H ₂₇ N ₅ O ₂ S .HCl
272392	CN	Me	CH ₂ Ph	SO ₂ Ph	1	R	C ₂₈ H ₂₇ N ₅ O ₂ S .HCl



272389: C25 H26 N4 O3 S . 2HCl

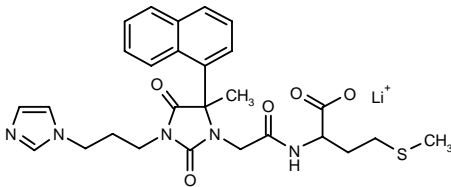
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bhide, R.S. et al. (Bristol-Myers Squibb Co.) *Inhibitors of farnesyl protein transferase.* WO 9901434.

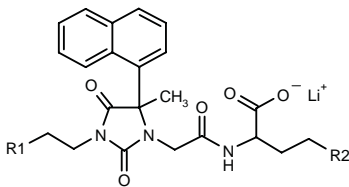
273008

2-[2-[3-[3-(1*H*-imidazol-1-yl)propyl]-5-methyl-5-(1-naphthyl)-2,4-dioxo-1-imidazolidinyl]acetamido]-4-(methylsulfonyl)butyric acid lithium salt

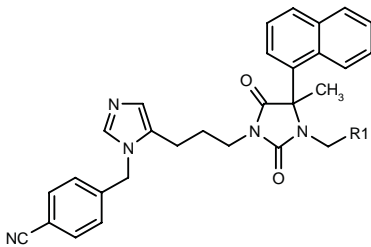


C27 H30 Li N5 O5 S; Mol wt: 543.5710

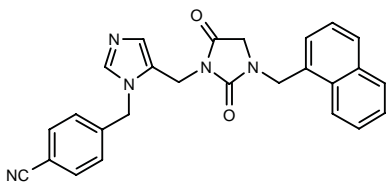
ACTION – Antineoplastic agent, a potent and selective protein farnesyltransferase inhibitor (IC₅₀ = 1 nM; IC₅₀ geranylgeranyltransferase > 10 μM). Within this series of hydantoin derivatives, the following are also included:



Compound	R1	R2	Formula
273009	5-imidazolyl-CH ₂	SO ₂ Me	C ₂₇ H ₃₀ LiN ₅ O ₇ S
273010	1-imidazolyl	SMe	C ₂₆ H ₂₈ LiN ₅ O ₅ S



Compound	R1	Formula
273011	Me	C ₃₀ H ₂₉ N ₅ O ₂
273012	CO ₂ Et	C ₃₂ H ₃₁ N ₅ O ₄
273013	CO ₂ Li	C ₃₀ H ₂₆ LiN ₅ O ₄
273014	CONHCH(CO ₂ Me)CH ₂ CH ₂ SMe	C ₃₆ H ₃₈ N ₆ O ₅ S
273015	CONHCH(CO ₂ Li)CH ₂ CH ₂ SMe	C ₃₅ H ₃₅ LiN ₆ O ₅ S



273016: C26 H21 N5 O2

SOURCE – LG Chemical.

REFERENCES

1. Lee, J.H. et al. (LG Chem Ltd.) *Hydantoin derivs. having an inhibitory activity for farnesyl transferase*. WO 9905117.

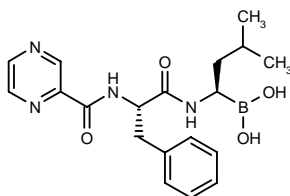
PS-341*

260757

[3-Methyl-1 (*R*)-(2-pyrazinylcarbonyl-L-phenylalanyl-amino)butyl]boronic acid

Pyrazin-2-ylcarbonyl-L-phenylalanyl-L-boroleucine

NSC-681239



C19 H25 B N4 O4; Mol wt: 384.2415

ACTION – Potent, small-molecule proteasome inhibitor ($K_i = 0.62$ nM against chymotrypsin-like proteolytic activity of rabbit muscle 20S proteasome) with high selectivity over other serine proteases such as human leukocyte elastase and thrombin ($K_i > 2000$ nM), human cathepsin G and human chymotrypsin ($K_i > 300$ nM). Compound inhibited the tumor necrosis factor (TNF- α)-stimulated activation of NF- κ B in primary human umbilical vein endothelial cells (HUVEC; IC_{50} approx. 0.5 μ M), and the subsequent transcription of genes regulated by NF- κ B and the expression of proinflammatory cytokines and cell adhesion molecules. *In vivo*, orally administered compound (0.3 mg/kg for 28 days) exhibited acute and chronic antiinflammatory activity in streptococcal cell wall-induced polyarthritis in rats, even when treatment was begun after disease onset, and it reduced the associated liver inflammation. It has also demonstrated antitumor activity and synergistic activity in combination with other chemotherapeutic agents and is suggested to have potential particularly in the treatment of refractory chronic lymphocytic leukemia (CLL). Currently undergoing phase I clinical trials in cancer patients.

SOURCES – National Cancer Institute, Bethesda, MD (US); ProScript.

REFERENCES

1. Adams, J. et al. (ProScript, Inc.) *Boronic ester and acid cpds., synthesis and uses*. JP 98510245, US 5780454, WO 9613266.
2. Adams, J. et al. *Dipeptide boronic acids: Selective proteasome inhibitors*. Proc Amer Assoc Cancer Res 1999, 40 Abst 2620.
3. Adams, J. et al. *Potent and selective inhibitors of the proteasome: Dipeptidyl boronic acids*. Bioorg Med Chem Lett 1998, 8(4): 333.

4. Chandra, J. et al. *Proteasome inhibitors induce apoptosis in glucocorticoid-resistant chronic lymphocytic leukemic lymphocytes*. Blood 1998, 92(11): 4220.

5. Chang, C.J.G. et al. *Multiple dose toxicity and proteasome inhibition of PS-341 (NSC-681239) in rats*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3416.

6. Elliott, P.J. et al. *Novel anti-cancer agents: PS-341, comparison with new proteasome inhibitors*. Proc Amer Assoc Cancer Res 1999, 40: Abst 836.

7. Kalogeris, T.J. et al. *Selective proteasome inhibitors lactacystin and PS-341 attenuate TNF-induced activation of endothelial cells*. FASEB J 1999, 13(4, Part 1): Abst 153.3.

8. Palombella, V.J. et al. *Role of the proteasome and NF-kappaB in streptococcal cell wall-induced polyarthritis*. Proc Natl Acad Sci USA 1998, 95(26): 15671.

9. *Novel anticancer agent from ProScript moves into clinical testing*. DailyDrugNews.com (Daily Essentials) 1998, Oct 16.

10. *ProScript and NCI enter collaboration for development of anticancer therapeutic*. DailyDrugNews.com (Daily Essentials) 1999, Jan 8.

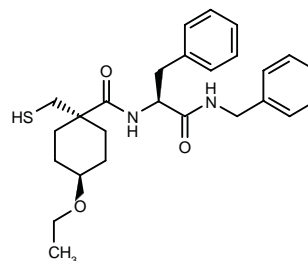
11. *Proscript initiates second phase I trial for PS-341*. DailyDrugNews.com (Daily Essentials) 1999, Feb 15.

*Identified compound **260757** Drug Data Report 1998, 020(04): 0358.

ANGIOGENESIS INHIBITORS

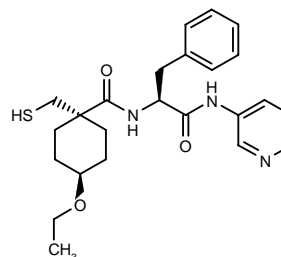
271999

*N*¹-(Benzyl)-*N*^α-[*trans*-4-ethoxy-1-(sulfonylmethyl)-1-cyclohexylcarbonyl]-L-phenylalanylamide



C26 H34 N2 O3 S; Mol wt: 454.6316

ACTION – Matrix metalloproteinase (MMP) inhibitor obtained by modifying a lead angiotensin-converting enzyme (ACE)/neutral endopeptidase (NEP) inhibitor template, with particularly good activity against gelatinase B (MMP-9; $IC_{50} = 26$ nM) relative to stromelysin (MMP-3; $IC_{50} = 207$ nM) and fibroblast collagenase (MMP-1; $IC_{50} = 823$ nM). Compound showed a good pharmacokinetic profile following oral administration in rats, with plasma levels at 4 h after administration of a dose of 75 μ mol/kg exceeding the IC_{50} values for MMP-3 and MMP-9. Another related compound is:



272000: C24 H31 N3 O3 S

Such compounds are considered to have potential in the treatment of disorders such as cancer, arthritis and multiple sclerosis.

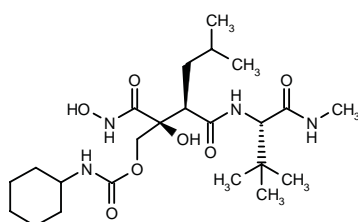
SOURCE – Novartis.

REFERENCES

1. Fink, C.A. (Novartis AG) *Certain cyclic thio subst. acylaminoacid amide derivs.* WO 9842662.
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272887

N-Cyclohexylcarbamic acid 3(*P*)-[*N*-[2,2-dimethyl-1(*S*)-(N-methylcarbamoyl)propyl]carbamoyl]-2(*S*)-hydroxy-2-(N-hydroxycarbamoyl)-5-methylhexyl ester



C23 H42 N4 O7; Mol wt: 486.6058

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as human interstitial collagenase (MMP-1; $K_i = 1.5$ nM), human gelatinase A (MMP-2; $K_i = 3.2$ nM) and human stromelysin 1 (MMP-3; $K_i = 23$ nM), reported to possess increased metabolic stability and superior pharmacokinetic properties as compared to previously known hydroxamic acid-type MMP inhibitors. *In vivo*, it was found to inhibit tumor growth in nude mice bearing human prostatic DU145 tumors (83% inhibition at 100 mg/kg i.p. b.i.d.).

SOURCE – Pharmacia & Upjohn.

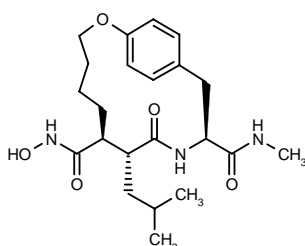
REFERENCES

1. Alpegiani, M. et al. (Pharmacia & Upjohn SpA) *Matrix metalloproteinase inhibitors.* WO 9833788.

A-177430

269780

(7*S*,8*R*,11*S*)-8-Isobutyl-*N*⁷-hydroxy-*N*¹¹-methyl-9-oxo-2-oxa-10-azabicyclo[11.2.2]heptadeca-1(15),13,16-triene-7,11-dicarboxamide



C22 H33 N3 O5; Mol wt: 419.5187

ACTION – Antiangiogenic agent, a potent matrix metalloproteinase (MMP) inhibitor with IC₅₀ values of 0.7-1.6 nM. Compound showed antitumor activity in mice implanted s.c. with human pancreatic carcinoma MiaPaCa, rat prostate carcinoma MatLyLu and human breast carcinoma MDA-468, inhibiting tumor growth and

prolonging survival. Additive effects were seen when compound was administered to mice together with cyclophosphamide. In mice implanted s.c. with matrigel plugs, it exhibited an antiangiogenic effect against neovascularization induced by fibroblast growth factor (FGF).

SOURCE – Abbott.

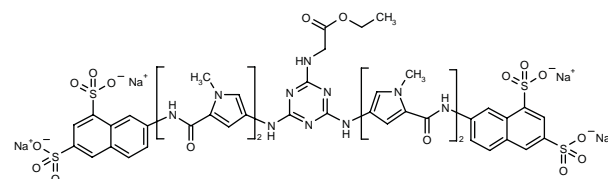
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2. Albert, D.H. et al. *Efficacy of a synthetic matrix metalloproteinase inhibitor A-177430 in a subcutaneous melanoma and an orthotopic brain tumor model.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2623.
3. Morgan, D.W. et al. *Macrocyclic succinamide hydroxamate MMP inhibitor demonstrates nanomolar potency and anti-tumor effects.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst P18.
4. Rabbani, S.A. et al. *A synthetic matrix metalloprotease inhibitor decreases tumor growth and metastases by inhibiting angiogenesis and promoting apoptosis in a syngeneic model of rat prostate cancer in vivo.* Proc Amer Assoc Cancer Res 1999, 40: Abst 3025.

PNU-157914

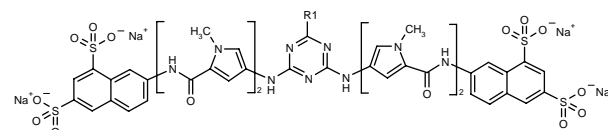
271808

N-[4,6-Bis[5-[*N*-[5-[*N*-(6,8-disulfonaphthalen-2-yl)carbamoyl]-1-methylpyrrol-3-yl]carbamoyl]-1-methylpyrrol-3-ylamino]-1,3,5-triazin-2-yl]glycine ethyl ester tetrasodium salt

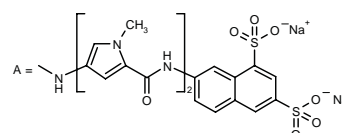


C51 H44 N14 Na4 O18 S4; Mol wt: 1361.2130

ACTION – Angiogenesis inhibitor, as demonstrated in the chorioallantoic membrane test, potentially useful in the treatment of conditions wherein the growth of new blood vessels is detrimental, e.g., chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. Compound also possesses tumor necrosis factor (TNF- α)-neutralizing activity, as well as anti-HIV activity. A representative compound within a series of specifically claimed substituted triazine derivatives, wherein the following are also included:



Compound	R1	Formula
PNU-157666 [271812]	A	C ₆₉ H ₅₄ N ₁₈ Na ₆ O ₂₄ S ₆
PNU-157015 [271813]	Cl	C ₄₇ H ₃₆ ClN ₁₃ Na ₄ O ₁₆ S ₄



SOURCE – Pharmacia & Upjohn.

REFERENCES

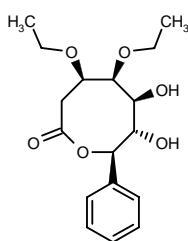
1. Mongelli, N. et al. (Pharmacia & Upjohn SpA) *Subst. triazine cpds. and their use in medicine*. WO 9900363.

OTHER ONCOLYTIC DRUGS

(+)-ALMUHEPTOLIDE A

271476

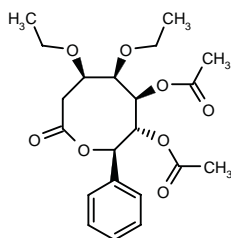
[4*R*-(4 α ,5 α ,6 α ,7 β ,8 α)]-4,5-Diethoxy-6,7-dihydroxy-8-phenyloxocan-2-one



C17 H24 O6; Mol wt: 324.3706

Yellowish oil, $[\alpha]_D + 11.7^\circ$ (c 1.8, EtOH).

ACTION – Potent and selective, noncompetitive inhibitor of the mammalian mitochondrial respiratory chain complex, a natural heptolide extracted from the stem bark of *Goniothalamus arvensis*. Compound inhibited integrated mitochondrial electron transport, measured as inhibition of NADH oxidase activity, with an IC_{50} of 4.4 μ M. Potentially useful as a cytotoxic and antitumor agent. Another heptolide extracted from the same source is:



271477: C21 H28 O8

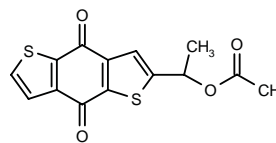
SOURCE – Universidad de Valencia, Valencia (ES).

REFERENCES

1. Bermejo, A. et al. *Enantiospecific semisynthesis of (+)-almuheptolide-A, a novel natural heptolide inhibitor of the mammalian mitochondrial respiratory chain*. J Med Chem 1998, 41(26): 5158.

270373

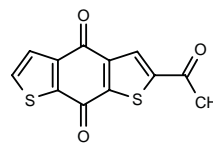
2-(1-Acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]-dithiophene-4,8-dione



C14 H10 O4 S2; Mol wt: 306.3610

Yellow solid, m.p. 174-6 °C.

ACTION – Antineoplastic agent with high overall potency against an NCI panel of tumor cell lines derived from leukemia, non-small-cell lung cancers, melanoma, breast cancers and ovarian cancers (mean GI_{50} = 40 nM). Selected from a series of thiophene derivatives as a candidate for further testing along with the following compound:



272733: C12 H6 O3 S2

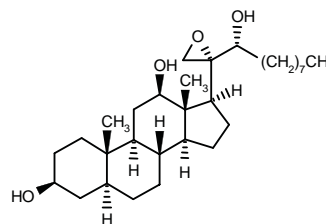
SOURCES – China Medical College, Taichung (TW); National Institutes of Health, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

REFERENCES

1. Chao, Y.-H. et al. *Synthesis and cytotoxicity of 2-acetyl-4,8-dihydrobenzodithiophene-4,8-dione derivatives*. J Med Chem 1998, 41(23): 4658.

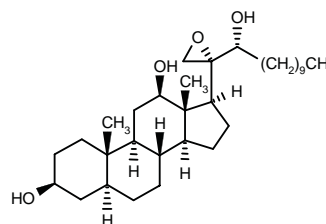
270999

17 α -[2(*S*)-[1(*R*)-Hydroxydecyl]oxiran-2-yl]-5 α -androstane-3 β ,12 β -diol



C31 H54 O4; Mol wt: 490.7636

ACTION – Antineoplastic agent able to prolong survival time in mice bearing leukemia L1210 (T/C x 100 > 370% at 6.25 mg/kg/day i.p. x 5). Another representative compound within this series of sterol derivatives is:



271000: C32 H56 O4

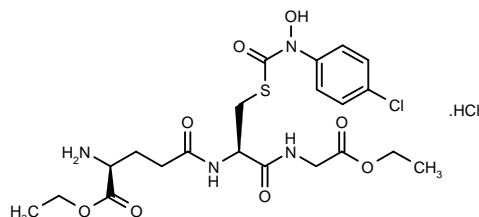
SOURCE – Taisho.

REFERENCES

1. Asanuma, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Sterol cpds.* JP 98310598.

272394

γ -L-Glutamyl-L-[S-[N-(4-chlorophenyl)-N-hydroxycarbamoyl]]cysteinyglycine diethyl ester hydrochloride



C21 H29 Cl N4 O8 S . HCl; Mol wt: 569.4600

ACTION – Competitive inhibitor of the methylglyoxal-detoxifying enzyme glyoxalase I (lactoylglutathione lyase; $K_i = 46$ nM against enzyme from human erythrocytes), considered a target for antitumor drug development, the diethyl ester prodrug of a glutathione derivative*. In murine leukemia L1210 and melanoma B16 cells, compound exerted growth-inhibitory ($GI_{50} = 7$ and 15 μ M, respectively) and cell-killing activity ($LC_{50} = 54$ and approx. 47 μ M, respectively); nonproliferating murine spleen lymphocytes were much less sensitive to the compound. Growth inhibition is associated with rapid diffusion of the compound into the cell, followed by enzymatic hydrolysis of the diethyl ester radicals. Compound was shown to undergo rapid deesterification in serum from inbred strains of mice, but slow deesterification in human serum.

SOURCE – University of Maryland, Baltimore, MD (US).

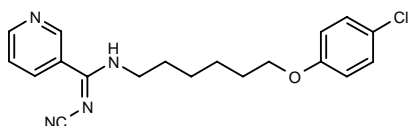
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2. Kavarana, M.J. et al. *Mechanism-based competitive inhibitors of glyoxalase I: Intracellular delivery, in vitro antitumor activities, and stabilities in human serum and mouse serum.* J Med Chem 1999, 42(2): 221.
3. Sharkey, E.M. et al. *Pharmacokinetics and antitumor properties of S-(N-p-chlorophenyl-N-hydroxycarbamoyl)glutathione diethyl ester in plasma esterase-deficient C57BL/6 mice bearing melanotic melanoma.* Proc Amer Assoc Cancer Res 1999, 40 Abst 2577.

*See **232441** (see **232318**) Drug Data Rep 1996, 018(05): 0471.

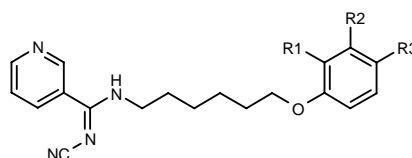
272460

N^1 -[6-(4-Chlorophenoxy)hexyl]- N^2 -cyano-3-pyridine-carboxamidine



C19 H21 Cl N4 O; Mol wt: 356.8549

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer. *In vitro*, it exhibited IC_{50} values of 39 and 350 nM, respectively, against the proliferation of human small cell lung carcinoma NYH and human breast cancer MCF-7 cells. *In vivo*, it was shown to increase the life span of Yoshida sarcoma-bearing rats, giving ILS values of 60 and 102%, respectively, at 10 and 30 mg/kg p.o. Other specifically claimed compounds from this series of cyanoamidines include the following:



Compound	R1	R2	R3	Formula
272461	OMe	H	H	$C_{20}H_{24}N_4O_2$
272462	H	-OCH2O-	H	$C_{20}H_{22}N_4O_3$
272463	NO2	H	H	$C_{19}H_{21}N_5O_3$

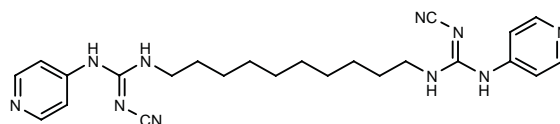
SOURCE – Leo Denmark.

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1. Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) *Cyanoamidines as cell proliferation inhibitors.* WO 9854147.

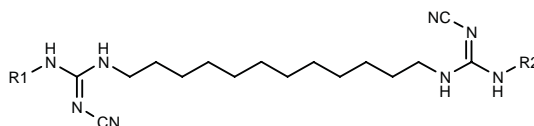
272464

N^1, N'^1 -(Decane-1,10-diyl)bis[N^2 -cyano- N^3 -(4-pyridyl)-guanidine]



C24 H32 N10; Mol wt: 460.5868

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells ($IC_{50} = 6.6$, 0.91 and 65 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1=R2	Formula
272465	3-Pyr	$C_{26}H_{36}N_{10}$
272466	4-Pyr	$C_{26}H_{36}N_{10}$

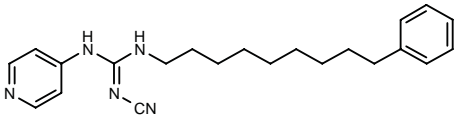
SOURCE – Leo Denmark.

REFERENCES

1. Petersen, H.J. and Schou, C. (Leo Pharmaceutical Products Ltd. A/S) *Cyanoguanidines as cell proliferation inhibitors.* WO 9854146.

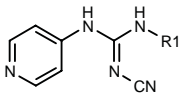
272467

N²-Cyano-N¹-(9-phenylnonyl)-N³-(4-pyridinyl)guanidine



C22 H29 N5; Mol wt: 363.5061

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells (IC₅₀ = 29, 5.3 and 5.8 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
272468	(CH2)5Ph	C ₁₈ H ₂₁ N ₅
272469	(CH2)8Ph	C ₂₁ H ₂₇ N ₅
272470	(CH2)13Ph	C ₂₆ H ₃₇ N ₅
272471	(Z)-(CH2)4CH=CHPh	C ₁₉ H ₂₁ N ₅
272472	(CH2)4-ethynyl-Ph	C ₁₉ H ₁₉ N ₅

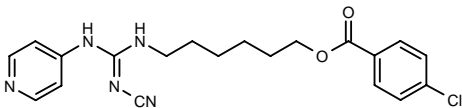
SOURCE – Leo Denmark.

REFERENCES

1. Ottosen, E.R. and Schou, C. (Leo Pharmaceutical Products Ltd. A/S) *Cyanoguanidines as cell proliferation inhibitors*. WO 9854145.

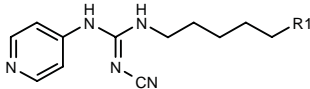
272473

4-Chlorobenzoic acid 6-[N²-cyano-N³-(4-pyridinyl)guanidino]hexyl ester



C20 H22 Cl N5 O2; Mol wt: 399.8798

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7 and human small cell lung carcinoma NYH cells (IC₅₀ = 2.2 and 1.7 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
272474	CH2NHCOPh	C ₂₀ H ₂₄ N ₆ O
272475	4-Cl-PhCO	C ₁₉ H ₂₀ ClN ₅ O
272476	4-Cl-PhCOCH2CH2	C ₂₁ H ₂₄ ClN ₅ O

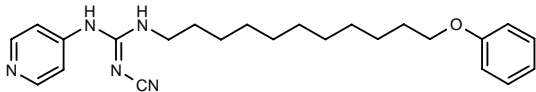
SOURCE – Leo Denmark.

REFERENCES

1. Schou, C. (Leo Pharmaceutical Products Ltd. A/S) *Cyanoguanidines as cell proliferation inhibitors*. WO 9854144.

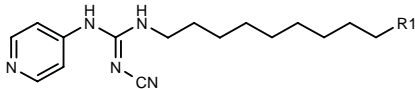
272477

N²-Cyano-N¹-(11-phenoxyundecyl)-N³-(4-pyridinyl)-guanidine



C24 H33 N5 O; Mol wt: 407.5587

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7 and human small cell lung carcinoma NYH cells (IC₅₀ = 21 and 4.5 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
272478	CH2OPh	C ₂₃ H ₃₁ N ₅ O
272479	OPh	C ₂₂ H ₂₉ N ₅ O

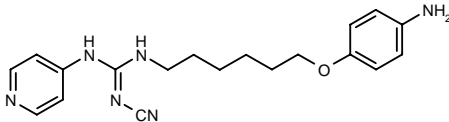
SOURCE – Leo Denmark.

REFERENCES

1. Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) *Cyanoguanidines as cell proliferation inhibitors*. WO 9854143.

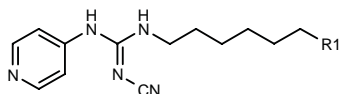
272480

N¹-[6-(4-Aminophenoxy)hexyl]-N²-cyano-N³-(4-pyridinyl)-guanidine



C19 H24 N6 O; Mol wt: 352.4396

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells (IC_{50} = 9.7, 4.8 and 59 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
272481	2-Naph	$C_{23}H_{25}N_5O$
272482	4-Me-2-oxo-2H-benzopyran-7-yl-O	$C_{23}H_{25}N_5O_3$
272483	N(CH ₂ Ph) ₂	$C_{27}H_{32}N_6$

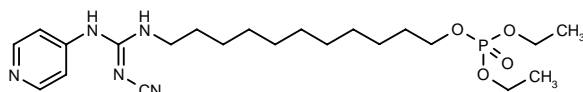
SOURCE – Leo Denmark.

REFERENCES

1. Schou, C. and Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) Cyanoguanidines as cell proliferation inhibitors. WO 9854142.

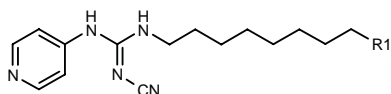
272484

Phosphoric acid 11-[N²-cyano-N³-(4-pyridinyl)guanidino]-undecyl diethyl ester



C₂₂ H₃₈ N₅ O₄ P; Mol wt: 467.5472

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells (IC_{50} = 1.7, 0.48 and 6.0 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
272485	2-THP-O(CH ₂) ₃	$C_{23}H_{37}N_5O_2$
272486	t-BuOCONH(CH ₂) ₄	$C_{24}H_{40}N_6O_2$
272487	t-BuOCONH	$C_{20}H_{32}N_6O_2$
272488	2-THP-O	$C_{20}H_{31}N_5O_2$
272489	CH ₂ OPO(OEt) ₂	$C_{20}H_{34}N_5O_4P$

SOURCE – Leo Denmark.

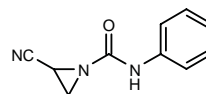
REFERENCES

1. Schou, C. and Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) Cyanoguanidines as cell proliferation inhibitors. WO 9854141.

AMP-404

272196

2-Cyano-N-phenylaziridine-1-carboxamide



C₁₀ H₉ N₃ O; Mol wt: 187.2011

ACTION – Antineoplastic agent structurally related to imexon with potent cytotoxicity against doxorubicin-sensitive, doxorubicin-resistant and mitoxantrone-resistant human breast cancer MCF-7 (IC_{50} = 0.5, 0.5 and 0.8 µg/ml, respectively), human colon cancer WiDr (IC_{50} = 0.9 µg/ml), human lung cancer A-549 (IC_{50} = 1.6 µg/ml), human malignant melanoma A-375 (IC_{50} = 2.1 µg/ml) and human ovarian cancer OVCAR-3 cells (IC_{50} = 1.3 µg/ml). Compound did not show crossresistance with imexon, as demonstrated *in vitro* against sensitive and imexon-resistant human myeloma 8226 cells (IC_{50} = 1.0 and 1.5 µg/ml, respectively, vs. 1.0 and 8.5 µg/ml, respectively, for imexon). Compound was tested *in vivo* in SCID mice bearing multidrug-resistant human myeloma 8226 tumors and was found to produce about a 50% reduction in tumor volume at 100 mg/kg/day x 4 weeks, although a reduction of about 15-20% in total body weight was observed; no reduction in tumor volume was observed at a dose of 50 mg/kg/day x 4 weeks.

SOURCE – University of Arizona, Tucson, AZ (US).

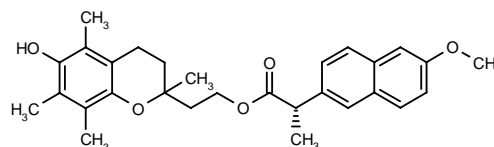
REFERENCES

1. Remers, W.A. et al. (University of Arizona) Novel cyanoaziridines for treating cancer. WO 9900120.

OCULAR MEDICATIONS

272421

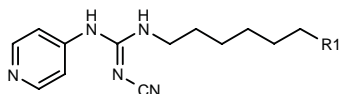
2(S)-(6-Methoxynaphthalen-2-yl)propionic acid 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-yl)ethyl ester



C₂₉ H₃₄ O₅; Mol wt: 462.5826

White solid, m.p. 99.5-101.5 °C.

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells (IC_{50} = 9.7, 4.8 and 59 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



Compound	R1	Formula
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272483	N(CH ₂ Ph) ₂	$C_{27}H_{32}N_6$

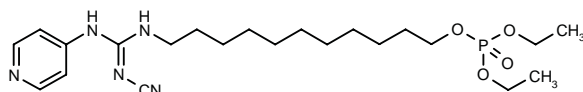
SOURCE – Leo Denmark.

REFERENCES

1. Schou, C. and Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) Cyanoguanidines as cell proliferation inhibitors. WO 9854142.

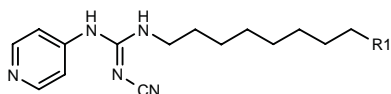
272484

Phosphoric acid 11-[N²-cyano-N³-(4-pyridinyl)guanidino]-undecyl diethyl ester



C₂₂ H₃₈ N₅ O₄ P; Mol wt: 467.5472

ACTION – Antiproliferative agent for the treatment or prevention of diseases characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and cancer, with potent *in vitro* cytotoxicity against human breast cancer MCF-7, human small cell lung carcinoma NYH and human non-small cell lung carcinoma NCI-H460 cells (IC_{50} = 1.7, 0.48 and 6.0 nM, respectively). Other specifically claimed compounds from this series of cyanoguanidines include the following:



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272489	CH ₂ OPO(OEt) ₂	$C_{20}H_{34}N_5O_4P$

SOURCE – Leo Denmark.

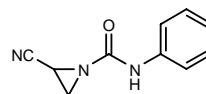
REFERENCES

1. Schou, C. and Ottosen, E.R. (Leo Pharmaceutical Products Ltd. A/S) Cyanoguanidines as cell proliferation inhibitors. WO 9854141.

AMP-404

272196

2-Cyano-N-phenylaziridine-1-carboxamide



C₁₀ H₉ N₃ O; Mol wt: 187.2011

ACTION – Antineoplastic agent structurally related to imexon with potent cytotoxicity against doxorubicin-sensitive, doxorubicin-resistant and mitoxantrone-resistant human breast cancer MCF-7 (IC_{50} = 0.5, 0.5 and 0.8 µg/ml, respectively), human colon cancer WiDr (IC_{50} = 0.9 µg/ml), human lung cancer A-549 (IC_{50} = 1.6 µg/ml), human malignant melanoma A-375 (IC_{50} = 2.1 µg/ml) and human ovarian cancer OVCAR-3 cells (IC_{50} = 1.3 µg/ml). Compound did not show crossresistance with imexon, as demonstrated *in vitro* against sensitive and imexon-resistant human myeloma 8226 cells (IC_{50} = 1.0 and 1.5 µg/ml, respectively, vs. 1.0 and 8.5 µg/ml, respectively, for imexon). Compound was tested *in vivo* in SCID mice bearing multidrug-resistant human myeloma 8226 tumors and was found to produce about a 50% reduction in tumor volume at 100 mg/kg/day x 4 weeks, although a reduction of about 15-20% in total body weight was observed; no reduction in tumor volume was observed at a dose of 50 mg/kg/day x 4 weeks.

SOURCE – University of Arizona, Tucson, AZ (US).

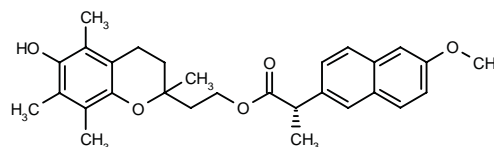
REFERENCES

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OCULAR MEDICATIONS

272421

2(S)-(6-Methoxynaphthalen-2-yl)propionic acid 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-yl)ethyl ester



C₂₉ H₃₄ O₅; Mol wt: 462.5826

White solid, m.p. 99.5-101.5 °C.

ACTION – Antioxidant–naproxen prodrug with potent antioxidant activity ($IC_{50} = 7.66 \mu M$ for inhibition of Fe^{2+} /ascorbate-induced oxidation of bovine heart membranes) and *in vitro* antiproliferative effect ($IC_{50} = 12.9 \mu M$ in human lung microvascular endothelial cells [HMVEC-L]). Its antiproliferative effect appears to be due to reversible inhibition of DNA synthesis (about 95% at 25 μM in HMVEC-L). Potentially useful as an angiostatic agent to reduce both postsurgical fibrovascular growth and lens fiber growth during vitreoretinal surgery. Studies are in progress to assess the antiinflammatory activity of the compound and its potential therapeutic utility as a component of an ocular irrigating solution to reduce complications during ocular surgery.

SOURCE – Alcon.

REFERENCES

1. Hellberg, M. et al. (Alcon Laboratories, Inc.) *Esters and amides of non-steroidal anti-inflammatory carboxylic acids which may be used as anti-oxidants, 5-lipoxygenase inhibitors and non-steroidal anti-inflammatory products*. EP 799219, JP 98511663, WO 9620187.

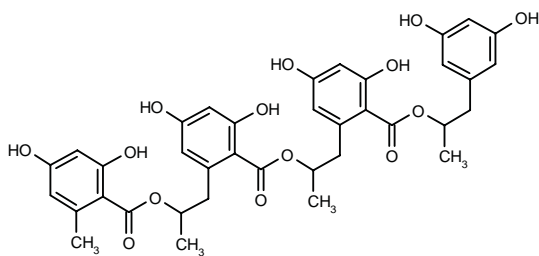
2. Hellberg, M.R. et al. *Novel esters and amides of nonsteroidal antiinflammatory carboxylic acids as antioxidants and antiproliferative agents*. J Med Chem 1999, 42(2): 267.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

271991

2-[2-[2-[2-(2,4-Dihydroxy-6-methylbenzoyloxy)propyl]-4,6-dihydroxybenzoyloxy]propyl]-4,6-dihydroxybenzoic acid 2-(3,5-dihydroxyphenyl)-1-methylethyl ester



C37 H38 O14; Mol wt: 706.6932

ACTION – Agent for the treatment of bone diseases such as osteoporosis and Paget's disease, a compound isolated from *Periconia* sp. Q47630 (FERM P-16245) that inhibits cathepsin L ($IC_{50} = 0.25 \mu M$ against enzyme from human kidney).

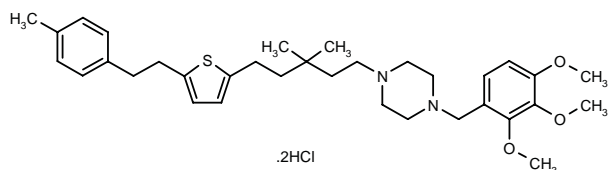
SOURCE – Yamanouchi.

REFERENCES

1. Hayata, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel cpds. or their salts, and cathepsin L inhibitors*. JP 98338661.

272330

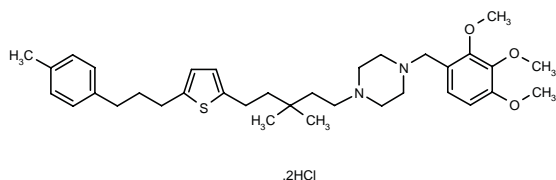
1-[3,3-Dimethyl-5-[5-[2-(4-methylphenyl)ethyl]thien-2-yl]-pentyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride



C34 H48 N2 O3 S . 2HCl; Mol wt: 637.7520

M.p. 222 °C.

ACTION – Inhibitor of bone resorption active against both retinoic acid- and parathyroid hormone (PTH)-induced bone resorption in cultured mouse calvariae, with IC_{50} values of 0.77 and 1.7 $\mu mol/l$, respectively. Compound had no significant effect on basal bone resorption, and its pharmacological profile suggests that it could act on a key step(s) in the activation of osteoclastic resorption. Another compound from this series of amino derivatives of phenylalkylthiophene is:



272331: C35 H50 N2 O3 S . 2HCl

SOURCE – Servier.

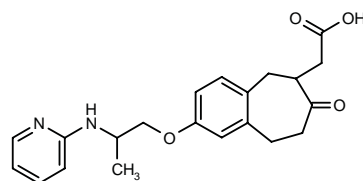
REFERENCES

1. Wierzbicki, M. et al. (ADIR et Cie.) *Thiophene derivs., process for their preparation and pharmaceutical compsns. containing them*. AU 9166901, EP 429370, FR 2655043, JP 91190872, US 5061704.

2. Wierzbicki, M. et al. *Amino derivatives of phenyl alkyl thiophene as inhibitors of bone resorption. Structure-activity relationship*. Arzneimittel-Forschung 1998, 48(8): 840.

272870

(±)-2-[7-Oxo-2-[2-(2-pyridinylamino)propoxy]-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]acetic acid



C21 H24 N2 O4; Mol wt: 368.4306

ACTION – Vitronectin ($\alpha v \beta 3$) receptor antagonist ($K_i = 23$ nM) with potential in the treatment of osteoporosis, angiogenesis, cancer, atherosclerosis, restenosis and inflammation. Another specifically claimed compound is:

ACTION – Antioxidant–naproxen prodrug with potent antioxidant activity ($IC_{50} = 7.66 \mu M$ for inhibition of Fe^{2+} /ascorbate-induced oxidation of bovine heart membranes) and *in vitro* antiproliferative effect ($IC_{50} = 12.9 \mu M$ in human lung microvascular endothelial cells [HMVEC-L]). Its antiproliferative effect appears to be due to reversible inhibition of DNA synthesis (about 95% at 25 μM in HMVEC-L). Potentially useful as an angiostatic agent to reduce both postsurgical fibrovascular growth and lens fiber growth during vitreoretinal surgery. Studies are in progress to assess the antiinflammatory activity of the compound and its potential therapeutic utility as a component of an ocular irrigating solution to reduce complications during ocular surgery.

SOURCE – Alcon.

REFERENCES

1. Hellberg, M. et al. (Alcon Laboratories, Inc.) *Esters and amides of non-steroidal anti-inflammatory carboxylic acids which may be used as anti-oxidants, 5-lipoxygenase inhibitors and non-steroidal anti-inflammatory products*. EP 799219, JP 98511663, WO 9620187.

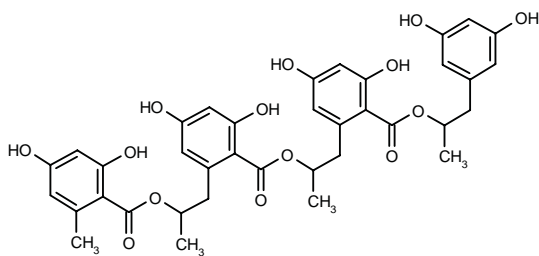
2. Hellberg, M.R. et al. *Novel esters and amides of nonsteroidal antiinflammatory carboxylic acids as antioxidants and antiproliferative agents*. J Med Chem 1999, 42(2): 267.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

271991

2-[2-[2-[2-(2,4-Dihydroxy-6-methylbenzoyloxy)propyl]-4,6-dihydroxybenzoyloxy]propyl]-4,6-dihydroxybenzoic acid 2-(3,5-dihydroxyphenyl)-1-methylethyl ester



C37 H38 O14; Mol wt: 706.6932

ACTION – Agent for the treatment of bone diseases such as osteoporosis and Paget's disease, a compound isolated from *Periconia* sp. Q47630 (FERM P-16245) that inhibits cathepsin L ($IC_{50} = 0.25 \mu M$ against enzyme from human kidney).

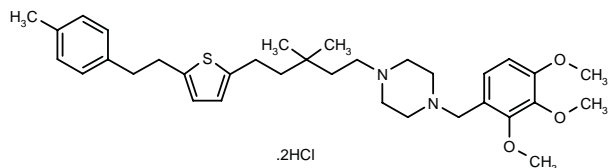
SOURCE – Yamanouchi.

REFERENCES

1. Hayata, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel cpds. or their salts, and cathepsin L inhibitors*. JP 98338661.

272330

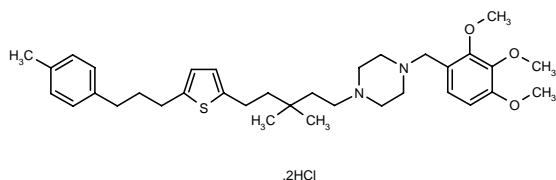
1-[3,3-Dimethyl-5-[5-[2-(4-methylphenyl)ethyl]thien-2-yl]pentyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride



C34 H48 N2 O3 S . 2HCl; Mol wt: 637.7520

M.p. 222 °C.

ACTION – Inhibitor of bone resorption active against both retinoic acid- and parathyroid hormone (PTH)-induced bone resorption in cultured mouse calvariae, with IC_{50} values of 0.77 and 1.7 $\mu mol/l$, respectively. Compound had no significant effect on basal bone resorption, and its pharmacological profile suggests that it could act on a key step(s) in the activation of osteoclastic resorption. Another compound from this series of amino derivatives of phenylalkylthiophene is:



272331: C35 H50 N2 O3 S . 2HCl

SOURCE – Servier.

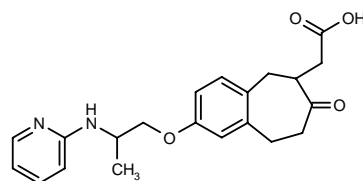
REFERENCES

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2. Wierzbicki, M. et al. *Amino derivatives of phenyl alkyl thiophene as inhibitors of bone resorption. Structure-activity relationship*. Arzneimittel-Forschung 1998, 48(8): 840.

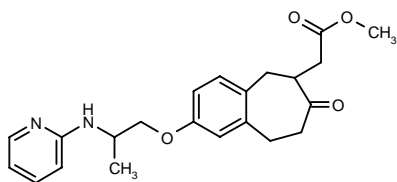
272870

(±)-2-[7-Oxo-2-[2-(2-pyridinylamino)propoxy]-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]acetic acid



C21 H24 N2 O4; Mol wt: 368.4306

ACTION – Vitronectin ($\alpha v \beta 3$) receptor antagonist ($K_i = 23$ nM) with potential in the treatment of osteoporosis, angiogenesis, cancer, atherosclerosis, restenosis and inflammation. Another specifically claimed compound is:



272871: C22 H26 N2 O4

SOURCE – SmithKline Beecham.

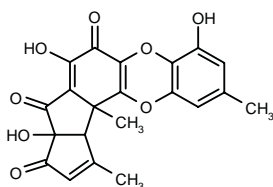
REFERENCES

1. Ku, T.W. (SmithKline Beecham Corp.) *Vitronectin receptor antagonist*. WO 9905107.

F-9775A

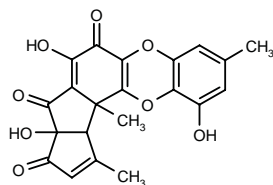
272783

2,5,12a-Trihydroxy-7,9b,10-trimethyl-9c,12a-dihydro-pentaleno[1,2-a]oxanthrene-1,3,12(9b*H*)-trione



C21 H16 O8; Mol wt: 396.3494

ACTION – Agent for the treatment of osteoporosis isolated from *Paecilomyces carneus* SANK 15996 (FERM BP-5916), an inhibitor of cathepsin K and L (IC_{50} = 28.8 and 98.9 mM, respectively). Another compound isolated from the same source is:



F-9775B [272785]: C21 H16 O8

SOURCE – Sankyo.

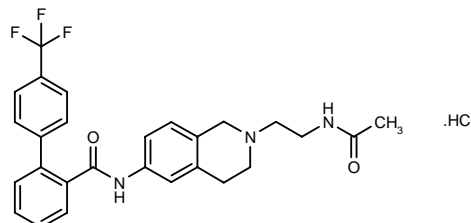
REFERENCES

1. Sato, A. et al. (Sankyo Co., Ltd.) *Novel substances, a F-9775A and B*. JP 99001480.

TREATMENT OF LIPOPROTEIN DISORDERS

271415

N-[2-[2-(Acetylamino)ethyl]-1,2,3,4-tetrahydro-6-isoquinolinyl]-4'-(trifluoromethyl)biphenyl-2-carboxamide hydrochloride



C27 H26 F3 N3 O2 . HCl; Mol wt: 517.9763

ACTION – Hypolipidemic and antiatherosclerotic agent that reduces serum cholesterol and triglyceride levels by virtue of its ability to inhibit microsomal triglyceride transfer protein (MTP) and apolipoprotein B (ApoB) secretion.

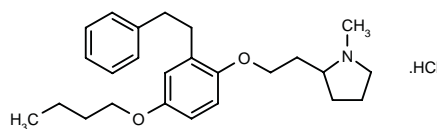
SOURCE – Pfizer.

REFERENCES

1. Chang, G. et al. (Pfizer Inc.) *4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-acetylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amide hydrochloride as apo B-secretion/MTP inhibitors*. EP 887345, JP 99060557.

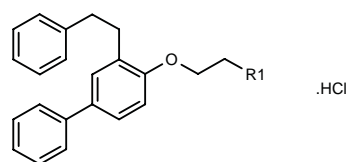
271965

2-[2-[4-Butoxy-2-(2-phenylethyl)phenoxy]ethyl]-1-methylpyrrolidine hydrochloride

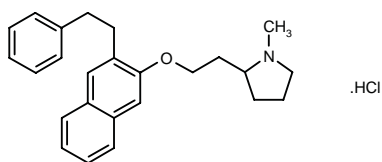


C25 H35 N O2 . HCl; Mol wt: 418.0174

ACTION – Hypolipidemic and antiatherosclerotic agent with 5-HT₂ receptor-antagonist (IC_{50} = 0.11 μ M for inhibition of 5-HT-induced rat caudal artery contractions) and squalene synthase-inhibitory activities (IC_{50} = 0.51 μ M against enzyme from rat liver microsomes). Within this series of phenoxyalkylamine derivatives, the following are also included:



Compound	R1	Formula
271966	1-Me-2-pyrrolidinyl	C ₂₇ H ₃₁ NO.HCl
271967	CH ₂ N(Me) ₂	C ₂₅ H ₂₉ NO.HCl



271968: C₂₅ H₂₉ N O . HCl

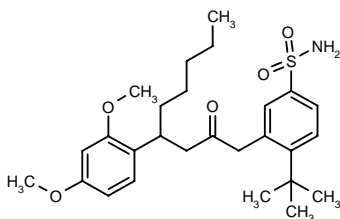
SOURCE – Sankyo.

REFERENCES

1. Fujimoto, K. et al. (Sankyo Co., Ltd.) *Phenoxyalkylamines*. JP 98316634.

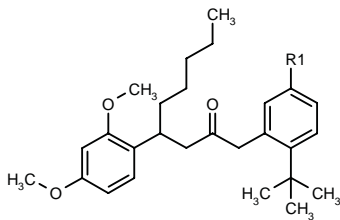
271969

4-*tert*-Butyl-3-[4-(2,4-dimethoxyphenyl)-2-oxononyl]-benzenesulfonamide



C₂₇ H₃₉ N O₅ S; Mol wt: 489.6731

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of ACAT (IC₅₀ = 2.8 ng/ml against enzyme from mouse macrophages). Other representative sulfide-containing compounds include the following:



Compound	R1	Formula
271970	CH ₂ SO ₂ Me	C ₂₉ H ₄₂ O ₅ S
271971	SO ₂ N(Me) ₂	C ₂₉ H ₄₃ NO ₅ S
271972	CH ₂ NHSO ₂ NH ₂	C ₂₈ H ₄₂ N ₂ O ₅ S
271973	CH ₂ SO ₂ NHMe	C ₂₉ H ₄₃ NO ₅ S

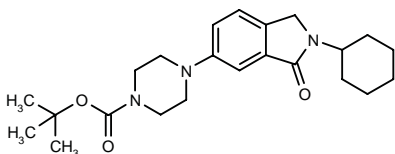
SOURCE – Sankyo.

REFERENCES

1. Yoshida, A. et al. (Sankyo Co., Ltd.) *Sulfide-containing cpds*. JP 98316648.

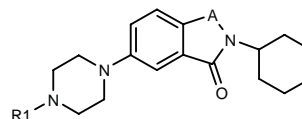
271979

4-(2-Cyclohexyl-3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)piperazine-1-carboxylic acid *tert*-butyl ester



C₂₃ H₃₃ N₃ O₃; Mol wt: 399.5317

ACTION – Hypolipidemic agent that acts by inhibiting the biosynthesis of triglycerides in the liver, as well as the secretion of lipoproteins containing apolipoprotein B from the liver (68 and 89% inhibition, respectively, at 3 μM in HepG2 cells). No deaths were observed in mice after a single oral dose of 200 mg/kg p.o. Other representative heterocyclic compounds include the following:



Compound	R1	A	Formula
271980	(E,E)-CH ₂ CH=C(Me)CH ₂ CH ₂ -CH=C(Me)CH ₂ CH ₂ CH=C(Me) ₂	-CH ₂ -	C ₃₃ H ₄₉ N ₃ O
271981	CH ₂ CH ₂ CH(Ph) ₂	-CH ₂ -	C ₃₃ H ₃₉ N ₃ O
271982	CH ₂ CH ₂ CH(Ph) ₂	-(CH ₂) ₂ -	C ₃₄ H ₄₁ N ₃ O

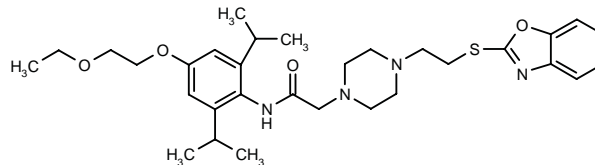
SOURCE – Meiji Seika.

REFERENCES

1. Ohkura, N. et al. (Meiji Seika Kaisha, Ltd.) *Nitrogenous heterocyclic cpds. and hyperlipemia remedy containing the same*. WO 9854135.

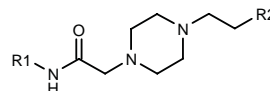
272096

2-[4-[2-(Benzoxazol-2-ylsulfanyl)ethyl]-1-piperazinyl]-*N*-[4-[2-(ethoxy)ethoxy]-2,6-diisopropylphenyl]acetamide



C₃₁ H₄₄ N₄ O₄ S; Mol wt: 568.7786

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of ACAT (IC₅₀ = 0.04 μM using enzyme from rat thoracic aorta microsomes; IC₅₀ = 0.21 μM using enzyme from rabbit small intestine); inhibition of ACAT activity was also determined in J774 and HepG2 cells (IC₅₀ = 0.014 and 0.82 μM, respectively). Within this series of cyclic diamine derivatives, the following are also included:



Compound	R1	R2	Formula
272097	2,6-(i-PrO) ₂ -Ph	2-benzoxazolyl-S	C ₂₇ H ₃₆ N ₄ O ₄ S
272098	2,6-(i-PrO) ₂ -Ph	2-benzothiazolyl-S	C ₂₇ H ₃₆ N ₄ O ₃ S ₂
272099	2,6-(i-PrO) ₂ -Ph	2-benzimidazolyl-S	C ₂₇ H ₃₇ N ₅ O ₃ S
272100	2,6-(i-PrO) ₂ -Ph	7-(CO ₂ Me)-2-benzoxazolyl-S	C ₂₉ H ₃₈ N ₄ O ₆ S
272101	2,6-(i-PrO) ₂ -Ph	4-(CO ₂ Me)-2-benzoxazolyl-S	C ₂₉ H ₃₈ N ₄ O ₆ S
272102	2,6-(i-PrO) ₂ -Ph	oxazolo[4,5-b]-pyridin-2-yl-S	C ₂₆ H ₃₅ N ₅ O ₄ S
272103	2,6-(i-PrO) ₂ -Ph	2-benzoxazolyl-SCH ₂	C ₂₈ H ₃₈ N ₄ O ₄ S
272104	2,6-(i-PrO) ₂ -Ph	7-(CO ₂ Me)-2-benzoxazolyl-SCH ₂	C ₃₀ H ₄₀ N ₄ O ₆ S
272105	6-Me-2,4-(MeS) ₂ -3-Pyr	oxazolo[4,5-b]-pyridin-2-yl-S	C ₂₂ H ₂₈ N ₆ O ₂ S ₃
272106	2,6-(i-Pr) ₂ -4-MeO-Ph	2-benzoxazolyl-S	C ₂₈ H ₃₈ N ₄ O ₃ S
272107	2,6-(i-Pr) ₂ -Ph	7-CF ₃ -2-benzoxazolyl-S	C ₂₈ H ₃₅ F ₃ N ₄ O ₂ S

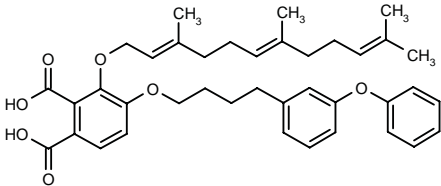
SOURCE – Kowa.

REFERENCES

1. Shibuya, K. et al. (Kowa Co., Ltd.) *Novel cyclic diamine cpds. and medicine containing the same*. WO 9854153.

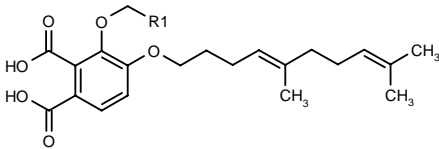
272144

4-[4-[3-(Phenyloxy)phenyl]butoxy]-3-[3,7,11-trimethyl-2(E),6(E),10-dodecatrienyloxy]phthalic acid

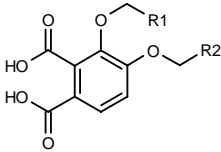


C39 H46 O7; Mol wt: 626.7854

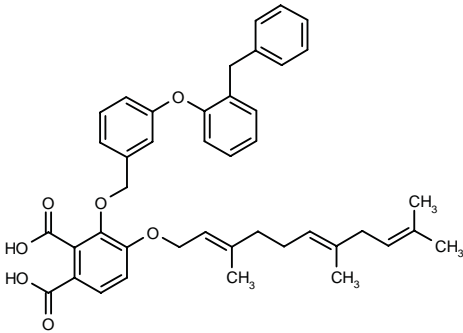
ACTION – Hypolipidemic and antifungal agent, a potent inhibitor of squalene synthase, as demonstrated using enzyme from *Aspergillus fumigatus* (IC₅₀ = 0.41 µg/ml), *Candida albicans* (IC₅₀ = 0.11 µg/ml) and rat liver (IC₅₀ = 0.72 µg/ml). Within this series of phthalic acid derivatives, the following are also included:



Compound	R1	Formula
272147	2-Naph-CH2CH2	C ₃₃ H ₃₈ O ₆
272148	CH=C(Me)CH2CH2- CH=C(Me)CH2CH2CH=C(Me)2	C ₃₅ H ₅₀ O ₆
272150	(CH2)4Ph	C ₃₁ H ₄₀ O ₆



Compound	R1	R2	Formula
272149	3-(PhO)-PhCH2	3-(PhO)-PhCH2	C ₃₆ H ₃₀ O ₈
272151	3-(PhO)-PhCH2CH2	3-(PhO)-PhCH2CH2	C ₃₈ H ₃₄ O ₈
272153	CH=C(Me)CH2CH2- CH=C(Me)CH2CH=C(Me)2	3-[2-(PhCH2)- -PhO]-Ph	C ₄₂ H ₄₄ O ₇
272154	CH=C(Me)CH2CH2- CH=C(Me)CH2CH=C(Me)2	2-Naph-CH2CH2	C ₃₅ H ₄₀ O ₆



272152: C42 H44 O7

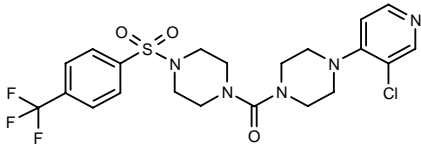
SOURCE – Nippon Kayaku.

REFERENCES

1. Ichikawa, Y. et al. (Nippon Kayaku Co., Ltd.) *Novel phthalic acid derivs*. JP 98316617.

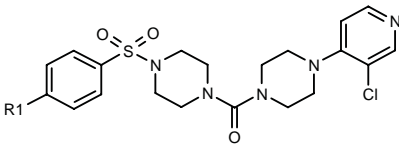
273208

1-[4-(3-Chloro-4-pyridinyl)-1-piperazinyl]-1-[4-[4-(trifluoromethyl)phenylsulfonyl]-1-piperazinyl]methanone



C21 H23 Cl F3 N5 O3 S; Mol wt: 517.9577

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of lanosterol synthase. Other specifically claimed compounds within this series of heterocyclic derivatives include the following:



Compound	R1	Formula
273209	F	C ₂₀ H ₂₃ ClFN ₅ O ₃ S
273210	H	C ₂₀ H ₂₄ ClN ₅ O ₃ S

SOURCE – Zeneca (AstraZeneca).

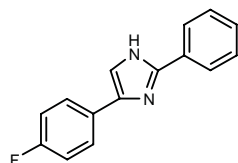
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

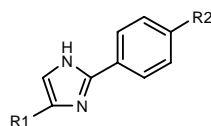
272274

4-(4-Fluorophenyl)-2-phenyl-1*H*-imidazole



C₁₅ H₁₁ F N₂; Mol wt: 238.2639

ACTION – Agent for the treatment or prevention of eating disorders such as obesity and bulimia, as well as certain cardiovascular disorders such as essential hypertension, that acts as a partial agonist or antagonist at neuropeptide Y (NPY) Y₅ receptors. Within this series of diarylimidazole derivatives, the following are also included:



Compound	R1	R2	Formula
272275	3-MeO-Ph	H	C ₁₆ H ₁₄ N ₂ O
272276	4-Cl-Ph	H	C ₁₅ H ₁₁ ClN ₂
272277	3-AcNH-Ph	H	C ₁₇ H ₁₅ N ₃ O
272278	1,4-benzodioxan-6-yl	F	C ₁₇ H ₁₃ FN ₂ O ₂
272279	4-Pr-3,4-dihydro-2H-1,4-benzoxazin-7-yl	H	C ₂₀ H ₂₁ N ₃ O
272280	3-[N(Me)2CH2]-Ph	H	C ₁₈ H ₁₉ N ₃

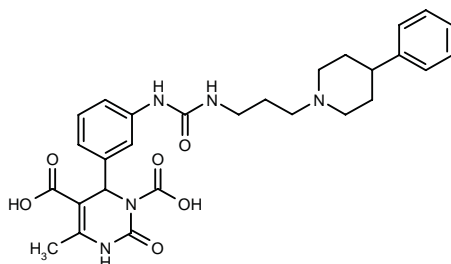
SOURCES – Neurogen; Pfizer.

REFERENCES

1. Thurkauf, A. et al. (Neurogen Corp.;Pfizer Inc.) *Certain diarylimidazole derivs.; a new class of NPY specific ligands*. WO 9901128.

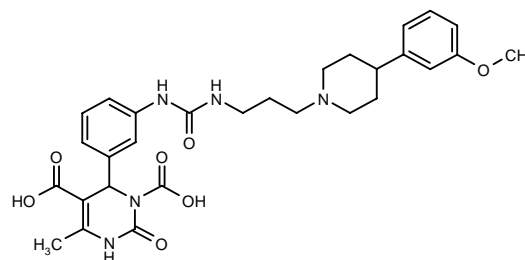
273222

4-Methyl-2-oxo-6-[3-[3-(4-phenyl-1-piperidinyl)-propyl]ureido]phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylic acid



C₂₈ H₃₃ N₅ O₆; Mol wt: 535.5977

ACTION – Selective neuropeptide Y (NPY) Y₁ receptor antagonist with potential in the treatment of diseases associated with excess NPY such as eating disorders. Another specifically claimed compound from this series of dihydropyrimidone derivatives is:



273223: C₂₉ H₃₅ N₅ O₇

SOURCE – Bristol-Myers Squibb.

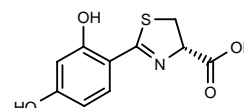
REFERENCES

1. Bruce, M.A. et al. (Bristol-Myers Squibb Co.) *Dihydropyrimidone derivs. as NPY antagonists*. US 5889016, WO 9833791.

TREATMENT OF POISONING AND DRUG DEPENDENCY

272065

2-(2,4-Dihydroxyphenyl)-4,5-dihydrothiazole-4(*S*)-carboxylic acid



C₁₀ H₉ N O₄ S; Mol wt: 239.2501

ACTION – Iron chelator, a desferrithiocin analogue with less oral efficiency than the parent compound in clearing iron from non-iron-overloaded, bile duct-cannulated rats (2.4% and 5.5%, respectively, at 150 µmol/kg p.o.); 100% was excreted in the bile. In iron-overloaded *Cebus apella* monkeys, compound was about 4-fold less effective than desferrithiocin (4.2% efficiency at the dose of 150 µmol/kg p.o.); 70% of the iron was cleared in stools and 30% in urine. However, contrary to the parent compound, it was devoid of systemic toxicity in rats, no deaths or histopathological abnormalities being seen in a short-term toxicity study (10 days' oral administration at 384 µmol/kg) or in an expanded-dosing protocol (32 days' oral administration at 250 µmol/kg).

SOURCE – University of Florida, Gainesville, FL (US).

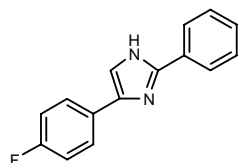
REFERENCES

1. Bergeron, R.J. et al. *Desazadesmethyldesferrithiocin analogues as orally effective iron chelators*. J Med Chem 1999, 42(1): 95.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

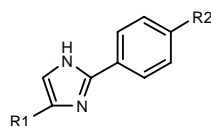
272274

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272277	3-AcNH-Ph	H	C ₁₇ H ₁₅ N ₃ O
272278	1,4-benzodioxan-6-yl	F	C ₁₇ H ₁₃ FN ₂ O ₂
272279	4-Pr-3,4-dihydro-2H-1,4-benzoxazin-7-yl	H	C ₂₀ H ₂₁ N ₃ O
272280	3-[N(Me)2CH2]-Ph	H	C ₁₈ H ₁₉ N ₃

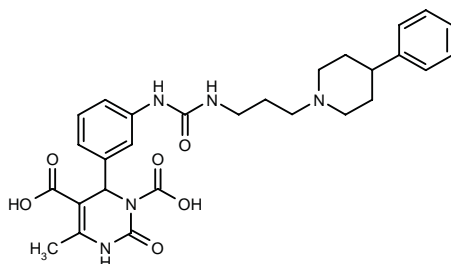
SOURCES – Neurogen; Pfizer.

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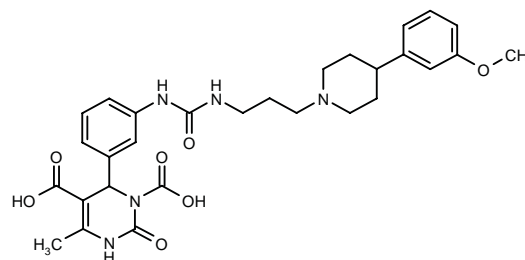
273222

4-Methyl-2-oxo-6-[3-[3-(4-phenyl-1-piperidinyl)-propyl]ureido]phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylic acid



C₂₈ H₃₃ N₅ O₆; Mol wt: 535.5977

ACTION – Selective neuropeptide Y (NPY) Y₁ receptor antagonist with potential in the treatment of diseases associated with excess NPY such as eating disorders. Another specifically claimed compound from this series of dihydropyrimidone derivatives is:



273223: C₂₉ H₃₅ N₅ O₇

SOURCE – Bristol-Myers Squibb.

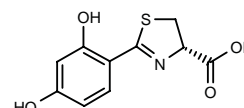
REFERENCES

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TREATMENT OF POISONING AND DRUG DEPENDENCY

272065

2-(2,4-Dihydroxyphenyl)-4,5-dihydrothiazole-4(*S*)-carboxylic acid



C₁₀ H₉ N O₄ S; Mol wt: 239.2501

ACTION – Iron chelator, a desferrithiocin analogue with less oral efficiency than the parent compound in clearing iron from non-iron-overloaded, bile duct-cannulated rats (2.4% and 5.5%, respectively, at 150 µmol/kg p.o.); 100% was excreted in the bile. In iron-overloaded *Cebus apella* monkeys, compound was about 4-fold less effective than desferrithiocin (4.2% efficiency at the dose of 150 µmol/kg p.o.); 70% of the iron was cleared in stools and 30% in urine. However, contrary to the parent compound, it was devoid of systemic toxicity in rats, no deaths or histopathological abnormalities being seen in a short-term toxicity study (10 days' oral administration at 384 µmol/kg) or in an expanded-dosing protocol (32 days' oral administration at 250 µmol/kg).

SOURCE – University of Florida, Gainesville, FL (US).

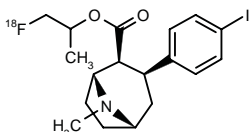
REFERENCES

1. Bergeron, R.J. et al. *Desazadesmethyldesferrithiocin analogues as orally effective iron chelators*. J Med Chem 1999, 42(1): 95.

DIAGNOSTIC AGENTS

271986

3*exo*-(4-Iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid 2-[¹⁸F]fluoro-1-methylethyl ester



C₁₈ H₂₃ F I N O₂; Mol wt: 430.2847

ACTION – Labeled cocaine analogue for use in positron emission tomography (PET) imaging of the brain, in particular those regions rich in dopaminergic neurons, for the differential diagnosis of Parkinson's disease and monitoring of cocaine addiction and the treatment thereof. In a binding assay, compound was shown to bind to the dopamine transporter (DAT) with a K_i of 1.13 nM using [³H]-Win-35428 as the radioligand and rat striatal homogenates.

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

1. Goodman, M.M. et al. (Emory University) *Labeled cocaine analogs*. US 5864038.

NC-100150

251676

Suspension of ultrasmall superparamagnetic iron oxide particles each comprising a single iron oxide crystal (5-7 nm in diameter) stabilized with a carbohydrate-polyethylene glycol coat binder with an approximate particle diameter of 20 nm

Clariscan™
PEG-Ferron

ACTION – Magnetic resonance imaging (MRI) blood pooling agent consisting of starch-coated ultrasmall superparamagnetic iron oxide particles. In pigs, 3D MRI with compound permitted the detection and localization of intraluminal bleeding both in small bowel and in colon, as well as of hepatic bleeding sites and pulmonary hemorrhage, with a sensitivity comparable to radionuclide scintigraphy. Experimental MR coronary angiography with NC-100150 in pigs permitted better visualization of coronary arteries and branches than X-ray angiography, especially in segments distal to occlusion. In dog, pulmonary MR angiography with compound at doses of 0.5-8 mg Fe/kg revealed complete visualization of central, lobar and segmental pulmonary vessels. In phase II clinical trials, it was shown that pulmonary MR angiography with NC-100150 allowed image acquisition in a tolerable breathholding time (17-25 s) and provided better visualization of partial thrombosis in the main pulmonary branches than conventional angiography.

SOURCE – Nycomed Amersham.

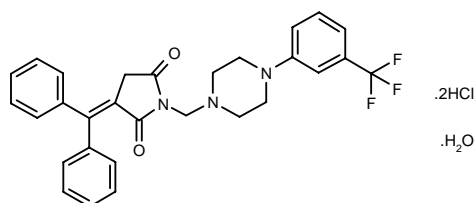
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1. Bremerich, J. et al. *Pulmonary MR angiography with blood pool contrast agent: Effects of dose, echo time, and flip angle on vascular enhancement*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abstr.
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4. Hilfiker, P.R. et al. *Intestinal and peritoneal bleeding: Detection with an intravascular contrast agent and fast three-dimensional MR imaging - Preliminary experience from an experimental study*. Radiology 1998, 209(3): 769.
5. Johansson, L.O. et al. *High resolution magnetic resonance coronary angiography of the entire heart using a new blood-pool agent NC100150 injection: Comparison with X-ray angiography*. Circulation 1998, 98(17, Suppl.): Abstr 2700.
6. Saeed, M. et al. *Value of blood pool contrast agents in magnetic resonance angiography of the pelvis and lower extremities*. Eur Radiol 1998, 8(6): 1047.
7. Weishaupt, D. et al. *Pulmonary hemorrhage: Imaging with a new MR blood pool agent in conjunction with breathheld 3D MRA - An experimental study*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abstr.
8. Nycomed Amersham: *nine-month highlights*. DailyDrugNews.com (Daily Essentials) 1998, April 15.
9. Nycomed Annual Report 1996

PHARMACOLOGICAL TOOLS

272052^{1,2}

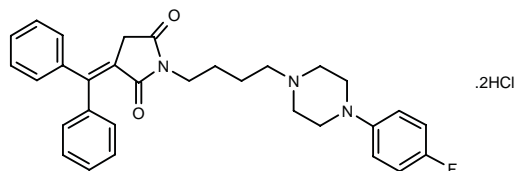
3-(Diphenylmethylidene)-1-[4-[3-(trifluoromethyl)-phenyl]piperazin-1-ylmethyl]-2,5-pyrrolidinedione dihydrochloride hydrate



C₂₉ H₂₆ F₃ N₃ O₂ . 2HCl . H₂O; Mol wt: 596.4740

M.p. 174-5 °C.

ACTION – High-affinity ligand for the 5-HT_{1A} receptor (K_i = 59.6 nM against [³H]-8-OH-DPAT binding in rat cerebral cortex membranes) with high selectivity relative to both α_1 -adrenoceptors and dopamine D₂ receptors (K_i > 1000 nM). Functional agonist activity at postsynaptic 5-HT_{1A} receptors was indicated by inhibition of forskolin-stimulated adenylyl cyclase activity in rat hippocampal slices (approx. 80% at 100 μ M). Another related imide-aryl piperazine is:

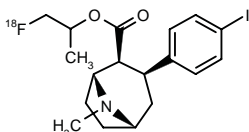


272054:² C₃₁ H₃₂ F N₃ O₂ . 2HCl

DIAGNOSTIC AGENTS

271986

3*exo*-(4-Iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2*exo*-carboxylic acid 2-[¹⁸F]fluoro-1-methylethyl ester



C₁₈ H₂₃ F I N O₂; Mol wt: 430.2847

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SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

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NC-100150

251676

Suspension of ultrasmall superparamagnetic iron oxide particles each comprising a single iron oxide crystal (5-7 nm in diameter) stabilized with a carbohydrate-polyethylene glycol coat binder with an approximate particle diameter of 20 nm

Clariscan™
PEG-Ferron

ACTION – Magnetic resonance imaging (MRI) blood pooling agent consisting of starch-coated ultrasmall superparamagnetic iron oxide particles. In pigs, 3D MRI with compound permitted the detection and localization of intraluminal bleeding both in small bowel and in colon, as well as of hepatic bleeding sites and pulmonary hemorrhage, with a sensitivity comparable to radionuclide scintigraphy. Experimental MR coronary angiography with NC-100150 in pigs permitted better visualization of coronary arteries and branches than X-ray angiography, especially in segments distal to occlusion. In dog, pulmonary MR angiography with compound at doses of 0.5-8 mg Fe/kg revealed complete visualization of central, lobar and segmental pulmonary vessels. In phase II clinical trials, it was shown that pulmonary MR angiography with NC-100150 allowed image acquisition in a tolerable breathholding time (17-25 s) and provided better visualization of partial thrombosis in the main pulmonary branches than conventional angiography.

SOURCE – Nycomed Amersham.

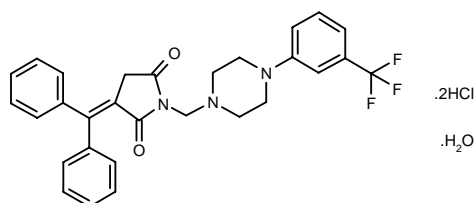
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2. Duerinckx, A.J. et al. *A phase II study of the use of a new MR blood pool agent (NC100150) for pulmonary angiography*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abstr.
3. Hilfiker, P.R. et al. *Detection of intestinal and peritoneal bleeding sites with a new MR blood pool contrast agent in conjunction with fast 3D MRI*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abstr.
4. Hilfiker, P.R. et al. *Intestinal and peritoneal bleeding: Detection with an intravascular contrast agent and fast three-dimensional MR imaging - Preliminary experience from an experimental study*. Radiology 1998, 209(3): 769.
5. Johansson, L.O. et al. *High resolution magnetic resonance coronary angiography of the entire heart using a new blood-pool agent NC100150 injection: Comparison with X-ray angiography*. Circulation 1998, 98(17, Suppl.): Abstr 2700.
6. Saeed, M. et al. *Value of blood pool contrast agents in magnetic resonance angiography of the pelvis and lower extremities*. Eur Radiol 1998, 8(6): 1047.
7. Weishaupt, D. et al. *Pulmonary hemorrhage: Imaging with a new MR blood pool agent in conjunction with breathheld 3D MRA - An experimental study*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abstr.
8. Nycomed Amersham: *nine-month highlights*. DailyDrugNews.com (Daily Essentials) 1998, April 15.
9. Nycomed Annual Report 1996

PHARMACOLOGICAL TOOLS

272052^{1,2}

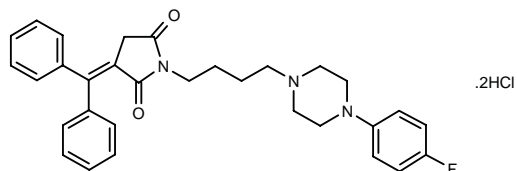
3-(Diphenylmethylidene)-1-[4-[3-(trifluoromethyl)-phenyl]piperazin-1-ylmethyl]-2,5-pyrrolidinedione dihydrochloride hydrate



C₂₉ H₂₆ F₃ N₃ O₂ . 2HCl . H₂O; Mol wt: 596.4740

M.p. 174-5 °C.

ACTION – High-affinity ligand for the 5-HT_{1A} receptor (K_i = 59.6 nM against [³H]-8-OH-DPAT binding in rat cerebral cortex membranes) with high selectivity relative to both α_1 -adrenoceptors and dopamine D₂ receptors (K_i > 1000 nM). Functional agonist activity at postsynaptic 5-HT_{1A} receptors was indicated by inhibition of forskolin-stimulated adenylyl cyclase activity in rat hippocampal slices (approx. 80% at 100 μ M). Another related imide-aryl piperazine is:



272054:² C₃₁ H₃₂ F N₃ O₂ . 2HCl

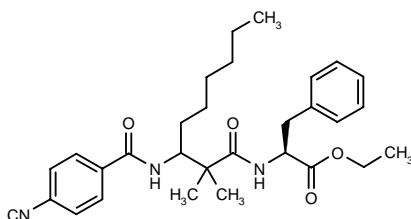
SOURCE – Universidad Complutense de Madrid, Madrid (ES).

REFERENCES

1. López Rodríguez, M.L. et al. (Universidad Complutense de Madrid) *New imidapiperazine derivs.* ES 2094690.
2. López-Rodríguez, M.L. et al. *Synthesis and structure-activity relationships of a new model of arylpiperazines. 4. 1-[ω-(4-Arylpiperazin-1-yl)alkyl]-3-(diphenylmethylene)-2,5-pyrrolidinediones and -3-(9H-fluoren-9-ylidene)-2,5-pyrrolidinediones: Study of the steric requirements of the terminal amide fragment on 5-HT_{1A} affinity/selectivity.* J Med Chem 1999, 42(1): 36.

272431

N-[3-(4-Cyanobenzamido)-2,2-dimethylnonanoyl]-L-phenylalanine ethyl ester



C30 H39 N3 O4; Mol wt: 505.6551

ACTION – Serine protease inhibitor with nanomolar activity against bovine α -chymotrypsin (IC_{50} = 2.6 nM; K_i = 45 nM), human cathepsin G (IC_{50} = 8.7 nM) and porcine elastase (IC_{50} = 7 nM), and less activity against trypsin (IC_{50} = 540 nM) and human chymase (IC_{50} = 440 nM). Compound inhibits α -chymotrypsin in a competitive and irreversible manner, probably interacting with the active site of the enzyme and forming a stable and irreversible acyl-enzyme. It appears to be a relatively slow-binding inhibitor. Potentially useful as a lead in the development of selective, stable ester-based serine protease inhibitors.

SOURCE – Nippon Steel.

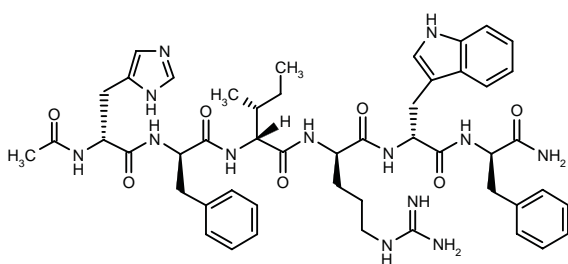
REFERENCES

1. Iijima, K. et al. *N-[2,2-Dimethyl-3-(N-(4-cyanobenzoyl)amino)nonanoyl]-L-phenylalanine ethyl ester as a stable ester-type inhibitor of chymotrypsin-like serine proteases: Structural requirements for potent inhibition of alpha-chymotrypsin.* J Med Chem 1999, 42(2): 312.

AC-178335

272751

N-Acetyl-D-histidyl-D-phenylalanyl-D-isoleucyl-D-arginyl-D-tryptophyl-D-phenylalaninamide



C49 H63 N13 O7; Mol wt: 946.1207

ACTION – Linear hexapeptide somatostatin antagonist with moderate selectivity for sst2 versus sst5 receptors (K_i = 172 vs. approx. 230 nM); in a functional assay in rat pituitary GH4C1 cells expressing the cloned rat sst2 receptor, compound exhibited full antagonist activity (IC_{50} = 5.1 μ M for reversing the MK-678-induced inhibition of forskolin-stimulated cAMP levels) and no agonist effects. In rats, at doses of 5-50 μ g i.v. it induced a short-lasting, dose-related and specific increase in growth hormone (GH) secretion, with or without pretreatment with the long-acting somatostatin agonist BIM-230; plasma prolactin or thyroid-stimulating hormone (TSH) levels were not affected by treatment with AC-178335. As its effects are small and transient, further work will be required to improve potency and specificity to explore potential clinical or diagnostic uses of such compounds. However, AC-178335 may be a useful tool for elucidating the role of somatostatin in the physiological control of GH secretion.

SOURCE – American Home Products.

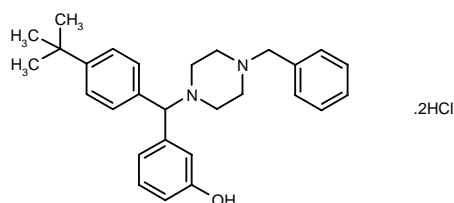
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1. Baumbach, W.R. and Houghten, R.A. (American Cyanamid Co.) *Peptides useful as somatostatin antagonists.* EP 863156.
2. Baumbach, W.R. et al. *A linear hexapeptide somatostatin antagonist blocks somatostatin activity in vitro and influences growth hormone release in rats.* Mol Pharmacol 1998, 54(5): 864.

SL-3111

270619

4-Benzyl-1-(4-tert-butyl-3'-hydroxybenzhydryl)piperazine dihydrochloride



C28 H34 N2 O . 2HCl; Mol wt: 487.5114

White solid.

ACTION – Potent and selective, nonpeptide δ -opioid receptor agonist (IC_{50} = 8 nM) with 2000-fold selectivity over μ -opioid receptors (IC_{50} = 17 μ M). In functional assays, compound showed an agonist profile with high potency (EC_{50} = 85 nM in mouse vas deferens) and good selectivity relative to μ -receptors (EC_{50} = 39 μ M in guinea pig ileum). Potentially useful as a pharmacological tool for elucidating the stereochemical requirements for nonpeptide δ -opioid-selective ligands.

SOURCE – University of Arizona, Tucson, AZ (US).

REFERENCES

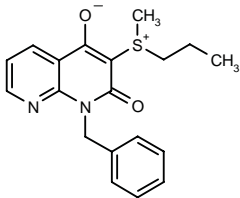
1. Liao, S. et al. *De novo design, synthesis, and biological activities of high-affinity and selective non-peptide agonists of the δ -opioid receptor.* J Med Chem 1998, 41(24): 4767.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

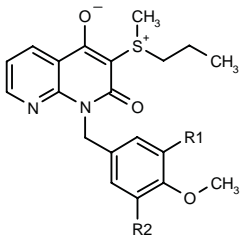
273154

1-Benzyl-3-[methyl(propyl)sulfonio]-2-oxo-1,2-dihydro-
[1,8]naphthyridin-4-olate



C19 H20 N2 O2 S; Mol wt: 340.4450

ACTION – Analgesic agent proven active in several rat models of pain following oral administration. Other representative compounds within this series of naphthyridine derivatives include the following:



Compound	R1	R2	Formula
273155	H	OMe	C ₂₁ H ₂₄ N ₂ O ₄ S
273156	OMe	OMe	C ₂₂ H ₂₆ N ₂ O ₅ S
273157	H	H	C ₂₀ H ₂₂ N ₂ O ₃ S

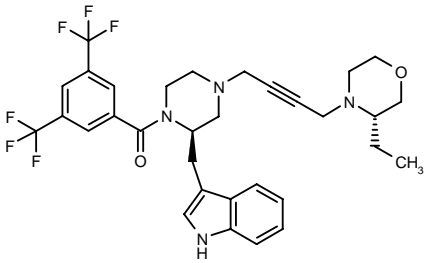
SOURCE – Otsuka.

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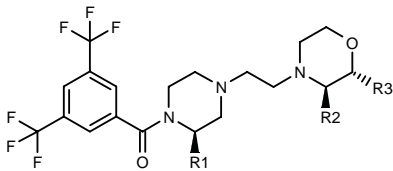
273900

1-[3,5-Bis(trifluoromethyl)phenyl]-1-[4-[4-[3(*S*)-ethyl-4-morpholinyl]-2-butynyl]-2(*R*)-(1*H*-indol-3-ylmethyl)-1-piperazinyl]methanone

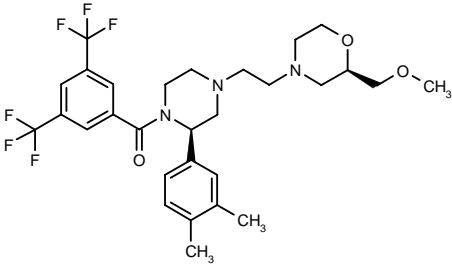


C32 H34 F6 N4 O2; Mol wt: 620.6346

ACTION – Tachykinin receptor antagonist with potential in the treatment of tachykinin-mediated disorders such as pain, asthma and inflammation. Other specifically claimed compounds from this series of aroyl-piperazine derivatives include the following:



Compound	R1	R2	R3	Formula
273901	3,4-(Me)2-Ph	H	CH2OMe	C ₂₉ H ₃₅ F ₆ N ₃ O ₃
273903	3,4-(Me)2-Ph	CH2OMe	H	C ₂₉ H ₃₅ F ₆ N ₃ O ₃
273906	3-indolyl-CH2	H	CH2OMe	C ₃₀ H ₃₄ F ₆ N ₄ O ₃
273910	3-indolyl-CH2	Et	H	C ₃₀ H ₃₄ F ₆ N ₄ O ₂



273904: C29 H35 F6 N3 O3

SOURCE – Fujisawa.

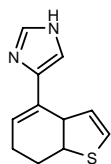
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RWJ-52353

273895

4-(3a,6,7,7a-Tetrahydrobenzothiophen-4-yl)-1*H*-imidazole



C₁₁ H₁₂ N₂ S; Mol wt: 204.2958

ACTION – Analgesic agent, a potent α_2 -adrenoceptor agonist with good selectivity over α_1 -adrenoceptors ($K_i = 1.5$ and 443 nM, respectively). *In vivo*, compound demonstrated analgesic activity in various pain models in rats and mice, with ED₅₀ values of 11.6, 15.1, 25.9 and 100.2 mg/kg p.o., respectively, in the mouse and rat abdominal irritant test, the mouse hot-plate test and the mouse tail-flick test. Selected as a potential candidate for the treatment of chronic pain from a series of bicyclic thiophenes.

SOURCE – R.W. Johnson.

REFERENCES

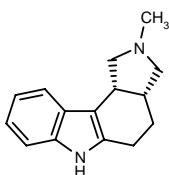
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2. Reitz, A.B. et al. *α_2 -Adrenoceptor agonists for the treatment of pain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 158.

RWJ-52807

273794

(3a*R*,10c*R*)-2-Methyl-1,2,3,3a,4,5,6,10c-octahydro-pyrrolo[3,4-*c*]carbazole



C₁₅ H₁₈ N₂; Mol wt: 226.3212

ACTION – Mixed α_2 -adrenoceptor agonist and α_1 -adrenoceptor antagonist with high affinity for these receptors ($K_i = 9.4$ and 61 nM, respectively); in functional assays, in addition to α_2 -agonist effects, it acted as an antagonist at α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors. *In vivo*, compound showed long-lasting analgesic activity in the hot-plate test without cardiovascular effects. Potentially useful for the treatment of chronic pain, e.g., in the topical treatment of postherpetic neuralgia.

SOURCE – R.W. Johnson.

REFERENCES

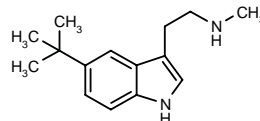
1. Reitz, A.B. et al. *α_2 -Adrenoceptor agonists for the treatment of pain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 158.

ANTIMIGRAINE DRUGS

MBT

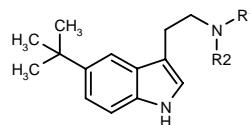
273130

2-(5-*tert*-Butyl-1*H*-indol-3-yl)-*N*-methyl-1-ethanamine



C₁₅ H₂₂ N₂; Mol wt: 230.3528

ACTION – Potent 5-HT_{1D} receptor agonist with sub-nanomolar affinity for the human receptor ($K_i = 0.45$ nM); compared to sumatriptan and naratriptan, it showed 5-10-fold higher potency and comparable selectivity over 5-HT_{1A} and 5-HT_{1B} receptors ($K_i = 6.1$ and 1.9 nM, respectively). In functional tests, compound displayed full agonist potency, inhibiting forskolin-stimulated adenylate cyclase in cell lines expressing the human 5-HT_{1D} receptor ($EC_{50} = 0.22$ nM; $E_{max} = 100\%$ of 5-HT). Potentially useful for the treatment of migraine. Other 5-*tert*-butyltryptamines include the following:



Compound	R1=R2	Formula
273131	H	C ₁₄ H ₂₀ N ₂
273132	Me	C ₁₆ H ₂₄ N ₂

SOURCES – Lilly; Synaptic.

REFERENCES

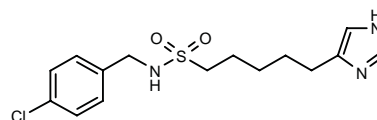
1. Xu, Y.-C. et al. *N-Methyl-5-*tert*-butyltryptamine: A novel, highly potent 5-HT_{1D} receptor agonist*. J Med Chem 1999, 42(3): 526.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

273272

N-(4-Chlorobenzyl)-5-(1*H*-imidazol-4-yl)pentane-1-sulfonamide

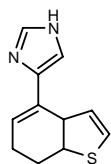


C₁₅ H₂₀ Cl N₃ O₂ S; Mol wt: 341.8610

RWJ-52353

273895

4-(3a,6,7,7a-Tetrahydrobenzothiophen-4-yl)-1*H*-imidazole



C₁₁ H₁₂ N₂ S; Mol wt: 204.2958

ACTION – Analgesic agent, a potent α_2 -adrenoceptor agonist with good selectivity over α_1 -adrenoceptors ($K_i = 1.5$ and 443 nM, respectively). *In vivo*, compound demonstrated analgesic activity in various pain models in rats and mice, with ED₅₀ values of 11.6, 15.1, 25.9 and 100.2 mg/kg p.o., respectively, in the mouse and rat abdominal irritant test, the mouse hot-plate test and the mouse tail-flick test. Selected as a potential candidate for the treatment of chronic pain from a series of bicyclic thiophenes.

SOURCE – R.W. Johnson.

REFERENCES

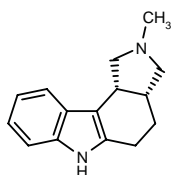
1. Jetter, M.C. et al. *Synthesis, α_2 adrenergic receptor binding affinity and in vivo activity of certain imidazole-substituted bicyclic thiophenes*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 111.

2. Reitz, A.B. et al. *α_2 -Adrenoceptor agonists for the treatment of pain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 158.

RWJ-52807

273794

(3a*R*,10c*R*)-2-Methyl-1,2,3,3a,4,5,6,10c-octahydro-pyrrolo[3,4-*c*]carbazole



C₁₅ H₁₈ N₂; Mol wt: 226.3212

ACTION – Mixed α_2 -adrenoceptor agonist and α_1 -adrenoceptor antagonist with high affinity for these receptors ($K_i = 9.4$ and 61 nM, respectively); in functional assays, in addition to α_2 -agonist effects, it acted as an antagonist at α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors. *In vivo*, compound showed long-lasting analgesic activity in the hot-plate test without cardiovascular effects. Potentially useful for the treatment of chronic pain, e.g., in the topical treatment of postherpetic neuralgia.

SOURCE – R.W. Johnson.

REFERENCES

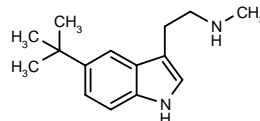
1. Reitz, A.B. et al. *α_2 -Adrenoceptor agonists for the treatment of pain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 158.

ANTIMIGRAINE DRUGS

MBT

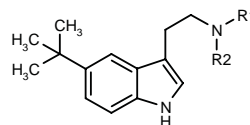
273130

2-(5-*tert*-Butyl-1*H*-indol-3-yl)-*N*-methyl-1-ethanamine



C₁₅ H₂₂ N₂; Mol wt: 230.3528

ACTION – Potent 5-HT_{1D} receptor agonist with sub-nanomolar affinity for the human receptor ($K_i = 0.45$ nM); compared to sumatriptan and naratriptan, it showed 5-10-fold higher potency and comparable selectivity over 5-HT_{1A} and 5-HT_{1B} receptors ($K_i = 6.1$ and 1.9 nM, respectively). In functional tests, compound displayed full agonist potency, inhibiting forskolin-stimulated adenylate cyclase in cell lines expressing the human 5-HT_{1D} receptor ($EC_{50} = 0.22$ nM; $E_{max} = 100\%$ of 5-HT). Potentially useful for the treatment of migraine. Other 5-*tert*-butyltryptamines include the following:



Compound	R1=R2	Formula
273131	H	C ₁₄ H ₂₀ N ₂
273132	Me	C ₁₆ H ₂₄ N ₂

SOURCES – Lilly; Synaptic.

REFERENCES

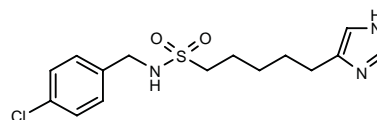
1. Xu, Y.-C. et al. *N-Methyl-5-*tert*-butyltryptamine: A novel, highly potent 5-HT_{1D} receptor agonist*. J Med Chem 1999, 42(3): 526.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

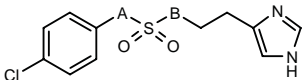
273272

N-(4-Chlorobenzyl)-5-(1*H*-imidazol-4-yl)pentane-1-sulfonamide



C₁₅ H₂₀ Cl N₃ O₂ S; Mol wt: 341.8610

ACTION – Histamine H₃ receptor antagonist, as demonstrated in binding and functional studies by pK_i values of 8.73 and 8.58, respectively, for inhibition of [³H]-(*R*)-α-methylhistamine binding in guinea pig ileal longitudinal muscle and guinea pig cortex preparations, and a pK_B value of 8.46 for inhibition of electrically stimulated contractions in guinea pig ileal longitudinal muscle strips. Potentially useful as a sedative, sleep regulator, anticonvulsant, regulator of hypothalamo-hypophyseal secretion, antidepressant, modulator of cerebral circulation, and for the treatment of asthma and irritable bowel syndrome. Other exemplified compounds from this series of 1*H*-4(5)-substituted imidazole derivatives include the following:



Compound	A	B	Formula
273273	-CH2NH-	-(CH2)2-	C ₁₄ H ₁₈ ClN ₃ O ₂ S
273274	-CH2NH-	-CH=CH-	C ₁₄ H ₁₆ ClN ₃ O ₂ S
273275	-CH2NH-	-CH2CH(OH)CH2-	C ₁₈ H ₂₀ ClN ₃ O ₃ S
273276	-CH2CH2NH-	-CH2CH(OH)CH2-	C ₁₈ H ₂₂ ClN ₃ O ₃ S
273277	-(CH2)2-	-(CH2)3-	C ₁₆ H ₂₁ ClN ₂ O ₂ S
273278	-CH2-	-(CH2)3-	C ₁₈ H ₁₉ ClN ₂ O ₂ S

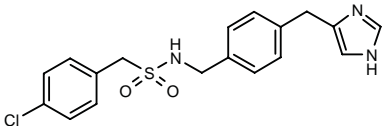
SOURCE – James Black Foundation.

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1. Tozer, M.J. et al. (James Black Foundation Ltd.) 1*H*-4(5)-Subst*d.* imidazole deriv*s.*, their preparation and their use as histamine H₃ receptor ligands. WO 9905114.

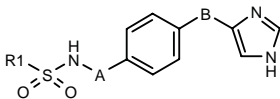
273454

4-Chloro-*N*-[4-(1*H*-imidazol-4-ylmethyl)benzyl]benzyl-sulfonamide

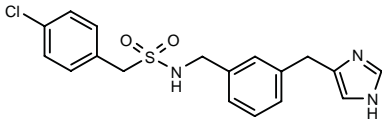


C18 H18 Cl N3 O2 S; Mol wt: 375.8782

ACTION – Histamine H₃ receptor ligand expected to behave as an antagonist or inverse agonist, as demonstrated in functional and binding assays using guinea pig ileum preparations (pK_B = 7.15; pK_i = 6.85), as well as in a binding assay using guinea pig cortex preparations (pK_i = 7.54). Potentially useful as a sedative, sleep regulator, anticonvulsant, hypothalamo-hypophyseal secretion regulator, antidepressant, cerebral circulation modulator, antiasthmatic agent and in the treatment of irritable bowel syndrome. Within this series of substituted imidazole derivatives, the following are also included:



Compound	R1	A	B	Formula
273456	2-Naph	-CH2-	CH2	C ₂₁ H ₁₉ N ₃ O ₂ S
273457	4-Cl-PhCH2NH	-CH2-	CH2	C ₁₈ H ₁₉ ClN ₄ O ₂ S
273458	4-Cl-PhCH2	bond	CH2	C ₁₇ H ₁₆ ClN ₃ O ₂ S
273459	4-Cl-PhCH2	bond	bond	C ₁₆ H ₁₄ ClN ₃ O ₂ S
273461	4-Cl-PhCH2	-(CH2)2-	CH2	C ₁₉ H ₂₀ ClN ₃ O ₂ S



273460: C18 H18 Cl N3 O2 S

SOURCE – James Black Foundation.

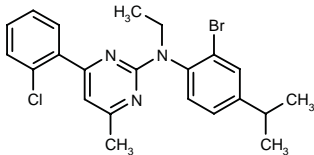
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ANXIOLYTICS

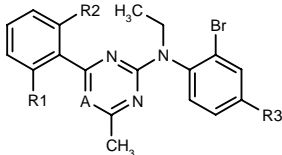
272362

N-(2-Bromo-4-isopropylphenyl)-*N*-[4-(2-chlorophenyl)-6-methyl-2-pyrimidinyl]-*N*-ethylamine

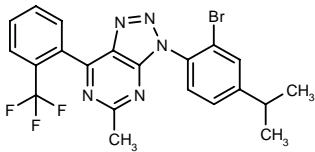


C22 H23 Br Cl N3; Mol wt: 444.8017

ACTION – Agent for the treatment of stress-related psychiatric and neurological disorders such as anxiety, depression and posttraumatic stress disorder, a corticotropin-releasing factor (CRF) antagonist. Within this series of specifically claimed aryl- and arylamino substituted heterocycles, the following are also included:



Compound	R1	R2	R3	A	Formula
272363	CF3	H	Br	CH	C ₂₀ H ₁₆ BrF ₃ N ₃
272364	CF3	H	Ac	CH	C ₂₂ H ₁₈ BrF ₃ N ₃ O
272365	CF3	H	i-Pr	N	C ₂₂ H ₂₂ BrF ₃ N ₄
272367	Cl	Cl	i-Pr	CH	C ₂₂ H ₂₂ BrCl ₂ N ₃



272366: C21 H17 Br F3 N5

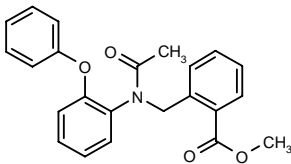
SOURCE – DuPont Pharmaceuticals.

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1. Cocuzza, A.J. et al. (DuPont Pharmaceuticals Co.) *Aryl- and arylamino-substd. heterocycles as corticotropin releasing hormone antagonists*. WO 9901439.

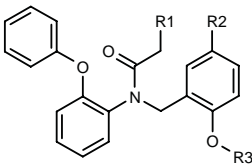
273140

2-[*N*-Acetyl-*N*-(2-phenoxyphenyl)aminomethyl]benzoic acid methyl ester



C23 H21 N O4; Mol wt: 375.4219

ACTION – Anxiolytic agent and antidepressant with high affinity for the mitochondrial diazepam binding inhibitor (DBI) receptor (MDR; IC₅₀ = 0.0643 nM). A representative compound from a series of aryloxyaniline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
273141	H	H	i-Pr	C ₂₄ H ₂₅ NO ₃
273142	H	OMe	Me	C ₂₃ H ₂₃ NO ₄
273143	Me	H	Me	C ₂₃ H ₂₃ NO ₃

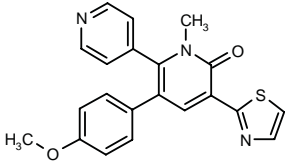
SOURCES – Nihon Nohyaku; Taisho.

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1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.;Nihon Nohyaku Co., Ltd.) *Aryloxyaniline derivs*. WO 9906353.

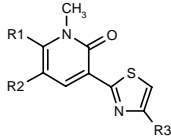
273336

5-(4-Methoxyphenyl)-1-methyl-6-(4-pyridinyl)-3-(2-thiazolyl)-2(1*H*)-pyridinone



C21 H17 N3 O2 S; Mol wt: 375.4503

ACTION – Agent for the treatment or prevention of CNS disorders such as anxiety, depression, convulsions, neuroses and migraine with high and selective affinity for the GABA_A receptor α2 and/or α3 subunits relative to the α1 subunit. Other specifically claimed compounds within this series of substituted pyridinyl-2(1*H*)-one derivatives include the following:



Compound	R1	R2	R3	Formula
273337	4-Pyr	4-MeO-Ph	Me	C ₂₂ H ₁₉ N ₃ O ₂ S
273338	5-Me-2-furyl	4-MeO-Ph	H	C ₂₁ H ₁₈ N ₂ O ₃ S
273339	4-pyrazinyl	4-MeO-Ph	Me	C ₂₁ H ₁₈ N ₄ O ₂ S
273340	4-pyrazinyl	2,4,6-(F)3-Ph	Me	C ₂₀ H ₁₃ F ₃ N ₄ OS
273341	Ph	OCH2Ph	Me	C ₂₃ H ₂₀ N ₂ O ₂ S
273342	4-Pyr	N(Me)CH2Ph	Me	C ₂₃ H ₂₂ N ₄ OS

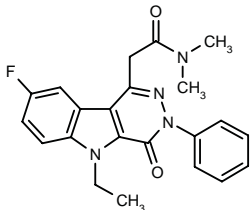
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Collins, I.J. et al. (Merck Sharp & Dohme Ltd.) *Substd. 1H-pyridinyl-2-ones as GABA_A α 2/3 ligands*. WO 9855480.

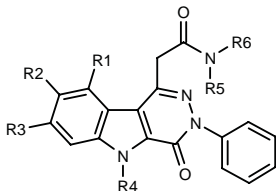
273569

2-(5-Ethyl-8-fluoro-4-oxo-3-phenyl-4,5-dihydro-3*H*-pyridazino[4,5-*b*]indol-1-yl)-*N,N*-dimethylacetamide



C22 H21 F N4 O2; Mol wt: 392.4319

ACTION – Agent with anxiolytic, anticonvulsant and hypnotic activity with affinity for the benzodiazepine binding site on the GABA_A receptor complex, reported to act as a complete or partial agonist. Other exemplified 4-oxo-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
273570	H	Cl	H	Me	-(CH2)4-		C ₂₃ H ₂₁ ClN ₄ O ₂
273571	H	H	H	Me	Me	Me	C ₂₁ H ₂₀ N ₄ O ₂
273572	H	H	H	Me	-(CH2)4-		C ₂₃ H ₂₂ N ₄ O ₂
273573	Br	H	H	Me	-(CH2)4-		C ₂₃ H ₂₁ BrN ₄ O ₂
273574	Br	H	H	Me	H	Me	C ₂₀ H ₁₇ BrN ₄ O ₂
273575	Me	H	H	Me	-(CH2)4-		C ₂₄ H ₂₄ N ₄ O ₂
273576	H	OCH2Ph	H	Me	-(CH2)4-		C ₃₀ H ₂₈ N ₄ O ₃
273577	H	Me	H	Me	Me	Me	C ₂₂ H ₂₂ N ₄ O ₂
273578	H	F	H	H	Me	Me	C ₂₀ H ₁₇ FN ₄ O ₂
273579	H	H	Cl	Me	Et	Et	C ₂₃ H ₂₃ ClN ₄ O ₂

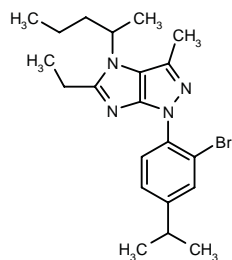
SOURCE – Synthélabo (Sanofi-Synthélabo).

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1. Evanno, Y. et al. (Synthélabo) 4-Oxo-3,5-dihydro-4H-pyridazino[4,5-b]-indole-1-acetamide derivs., their preparation and their application in therapy. WO 9906406.

273787

1-(2-Bromo-4-isopropylphenyl)-5-ethyl-3-methyl-4-(1-methylbutyl)-1,4-dihydroimidazo[4,5-c]pyrazole



C21 H29 Br N4; Mol wt: 417.3921

ACTION – Corticotropin-releasing factor (CRF) antagonist with high *in vitro* binding affinity for the CRF₁ receptor ($K_i = 4$ nM), potentially useful for the treatment of anxiety, depression and other stress-related disorders.

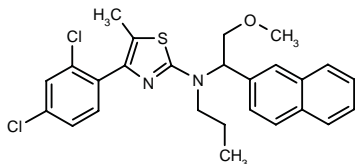
SOURCE – DuPont Pharmaceuticals.

REFERENCES

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2. Beck, J.P. et al. Imidazo[4,5-c]pyrazoles: A novel heterocyclic series of corticotropin releasing hormone (CRH R1) antagonists. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 001.
3. Beck, J.P. et al. Imidazo[4,5-c]pyrazoles as corticotropin releasing hormone (CRH R1) receptor antagonists: Detailed pyrazole SAR and synthesis. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 106.

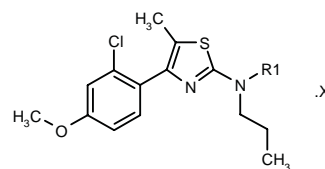
274006

N-[4-(2,4-Dichlorophenyl)-5-methylthiazol-2-yl]-N-[2-methoxy-1-(2-naphthyl)ethyl]-N-propylamine



C26 H26 Cl2 N2 O S; Mol wt: 485.4764

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of psychiatric disorders, anxiety, depression, anorexia nervosa, stress, sexual dysfunction, fertility disorders and Alzheimer's disease. Other specifically claimed compounds within this series of substituted 2-amino-4-phenylthiazoles include the following:



Compound	R1	X	Formula
274008	6-Me-5-isoquinolinyl	oxalate	C ₂₄ H ₂₄ ClN ₃ OS.C ₂ H ₂ O ₄
274010	6-MeO-5-isoquinolinyl		C ₂₄ H ₂₄ ClN ₃ O ₂ S
274014	1-MeO-2-Naph		C ₂₅ H ₂₅ ClN ₂ O ₂ S
274017	2,3-(Me)2-1-Naph	HCl	C ₂₆ H ₂₇ ClN ₂ OS.HCl
274018	2-Naph-CH(cyclopropyl)	HCl	C ₂₈ H ₂₉ ClN ₂ OS.HCl

SOURCE – Sanofi (Sanofi-Synthélabo).

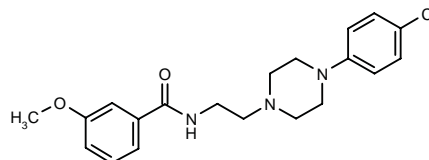
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1. Gully, D. et al. (Sanofi SA) Subst. 4-phenylaminothiazoles, their process of preparation and the pharmaceutical compsns. containing them. US 5880135, WO 9700868.

ANTIPSYCHOTIC DRUGS

270510

N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide



C20 H24 Cl N3 O2; Mol wt: 373.8816

M.p. 152 °C.

ACTION – Potent and selective dopamine D₄ receptor ligand with subnanomolar affinity for the cloned human D₄ receptor (IC₅₀ = 0.057 nM) and over 10,000-fold selectivity relative to the cloned human D₂ receptor (IC₅₀ > 1000 nM). Compound was also selective as regards both 5-HT_{1A} receptors and α₁-adrenoceptors (IC₅₀ = 220 and 270 nM, respectively). Potentially useful as an atypical anti-psychotic agent devoid of extrapyramidal and hormonal side effects.

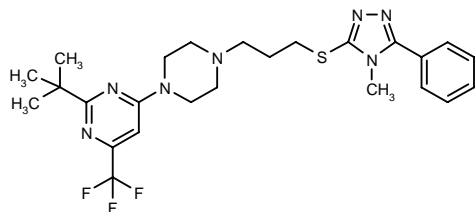
SOURCE – Università di Bari, Bari (IT).

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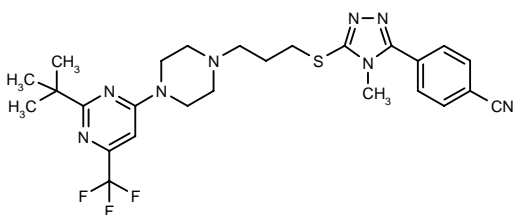
272544

2-(*tert*-Butyl)-4-[4-[3-(4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl)propyl]-1-piperazinyl]-6-(trifluoromethyl)-pyrimidine



C25 H32 F3 N7 S; Mol wt: 519.6368

ACTION – Antipsychotic agent with affinity for the dopamine D₃ receptor. Another compound within this series of triazole derivatives is :



272545: C26 H31 F3 N8 S

SOURCE – BASF.

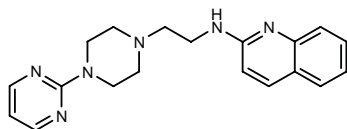
REFERENCES

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273036

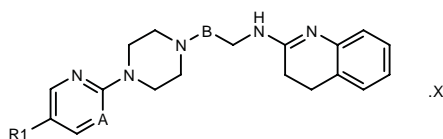
N-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]quinolin-2-amine

N-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-*N*-(2-quinolinyl)amine

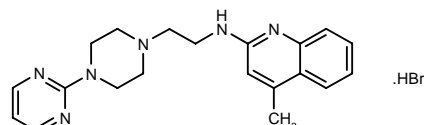


C19 H22 N6; Mol wt: 334.4248

ACTION – Antipsychotic agent with high affinity and selectivity for dopamine D₄ receptors as compared to dopamine D₂ receptors (K_i = 10 nM vs. 2720 nM in rat striatal homogenates) and some affinity for muscarinic M₁ and M₂ receptors (K_i = 264 and 299 nM, respectively). Within this series of specifically claimed 2-aminoalkyl-aminoquinoline derivatives, the following are also included:



Compound	R1	A	B	X	Formula
273037	H	CH	-CH2-		C ₂₀ H ₂₅ N ₅
273038	F	N	-CH2-		C ₁₉ H ₂₃ FN ₆
273040	H	N	-(CH2)2-	fumarate	C ₂₀ H ₂₆ N ₆ ·C ₄ H ₄ O ₄
273041	F	N	-(CH2)3-	HBr	C ₂₁ H ₂₇ FN ₆ ·HBr



273039: C20 H24 N6 . HBr

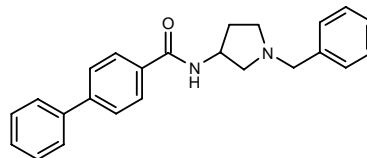
SOURCE – Neurogen.

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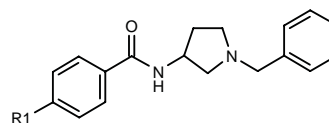
273071

N-(1-Benzyl-3-pyrrolidinyl)biphenyl-4-carboxamide



C24 H24 N2 O; Mol wt: 356.4666

ACTION – Antipsychotic agent with selective dopamine D₄ receptor-antagonist activity (K_i = 2.91 nM against [³H]-spiperone binding in HEK298 cells expressing the human receptor) and reduced side effects due to its relatively low affinity for dopamine D₂ receptors (D₂/D₄ = 261). The activity of test compound was also assessed in a functional assay, giving an IC₅₀ value of 1.5 μM for inhibition of forskolin-stimulated adenylyl cyclase activity. Within this series of specifically claimed benzamide derivatives, the following are also included.



Compound	R1	Formula
273072	4-CF3-Ph	C ₂₈ H ₂₃ F ₃ N ₂ O
273073	3-NH2-Ph	C ₂₄ H ₂₅ N ₃ O
273074	2-thienyl	C ₂₂ H ₂₂ N ₂ OS
273075	3-thienyl	C ₂₂ H ₂₂ N ₂ OS
273076	4-Cl-Ph	C ₂₄ H ₂₃ ClN ₂ O

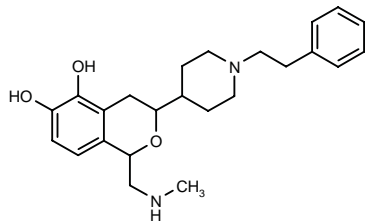
SOURCE – Hoechst Marion Roussel.

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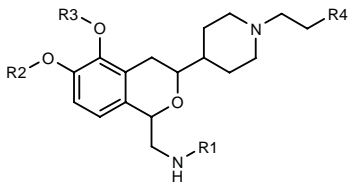
273238

1-(*N*-Methylaminomethyl)-3-[1-(2-phenylethyl)-4-piperidinyl]-3,4-dihydro-1*H*-2-benzopyran-5,6-diol



C24 H32 N2 O3; Mol wt: 396.5278

ACTION – Antipsychotic agent, a dopamine D₂ receptor antagonist proven to inhibit apomorphine-induced climbing in mice with an ED₅₀ value of 6.9 mg/kg i.p., compared to a value of 8.1 mg/kg i.p. for clozapine. A representative compound from a series of 3-(4-piperidinyl)-1*H*-2-benzopyran derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
273239	H	H	H	Ph	C ₂₃ H ₃₀ N ₂ O ₃
273240	CHO	Me	Me	4-F-PhCOCH ₂	C ₂₈ H ₃₅ FN ₂ O ₅
273241	H	H	H	6-F-3-benz-isoxazolyl-CH ₂	C ₂₅ H ₃₀ FN ₃ O ₄
273242	H	Ac	Ac	Ph	C ₂₇ H ₃₄ N ₂ O ₅

SOURCE – Hoechst Marion Roussel.

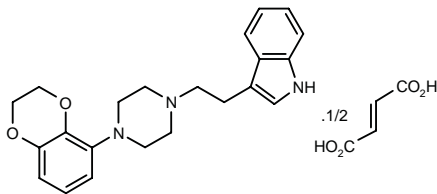
REFERENCES

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ANTIDEPRESSANTS

272852

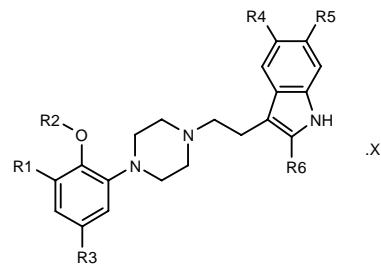
3-[2-[4-(2,3-Dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]-ethyl]-1*H*-indole hemifumarate



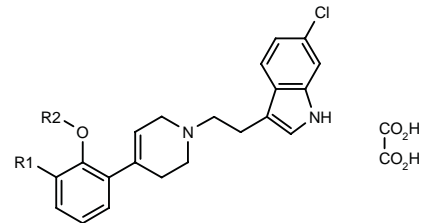
C22 H25 N3 O2 . 1/2 C4 H4 O4; Mol wt: 421.4943

ACTION – Antidepressant that displays 5-HT reuptake-inhibitory and 5-HT_{1A} receptor-antagonist activity (IC₅₀ = 2.9 nM against [³H]-5-CT binding to cloned human 5-HT_{1A} receptors stably expressed in transfected HeLa

cells). Its 5-HT reuptake-inhibitory activity was measured in rat brain synaptosome preparations (IC₅₀ = 3.5 nM vs. 0.29 nM for paroxetine) and its 5-HT_{1A} receptor-antagonist activity was also determined by measuring the ability of test compound to antagonize the 5-HT-induced inhibition of forskolin-induced cAMP accumulation (IC₅₀ = 160 nM). Within this series of specifically claimed indole and 2,3-dihydroindole derivatives, the following are also included:



Compound	R1,R2	R3	R4	R5	R6	X	Formula
272853	-OCH ₂ CH ₂ -	H	Br	H	H	oxalate	C ₂₂ H ₂₄ BrN ₃ O ₂ .C ₂ H ₂ O ₄
272854	-OCH ₂ CH ₂ -	H	H	H	Me	oxalate	C ₂₃ H ₂₇ N ₃ O ₂ .C ₂ H ₂ O ₄
272856	-OCH ₂ CH ₂ -	H	F	H	H	oxalate	C ₂₂ H ₂₄ FN ₃ O ₂ .C ₂ H ₂ O ₄
272857	-OCH ₂ CH ₂ -	H	H	Me	H	fumarate	C ₂₃ H ₂₇ N ₃ O ₂ .C ₄ H ₄ O ₄
272859	-OCH ₂ CH ₂ -	H	H	Cl	H	fumarate	C ₂₂ H ₂₄ FN ₃ O ₂ .C ₂ H ₂ O ₄
272860	-CH ₂ C(Me) ₂ -	Cl	H	H	H	fumarate	C ₂₃ H ₂₇ N ₃ O ₂ .C ₄ H ₄ O ₄



Compound	R1,R2	Formula
272855	-CH ₂ C(Me) ₂ -	C ₂₅ H ₂₇ ClN ₂ O ₂ .C ₂ H ₂ O ₄
272858	-OCH ₂ CH ₂ -	C ₂₃ H ₂₃ ClN ₂ O ₂ .C ₂ H ₂ O ₄

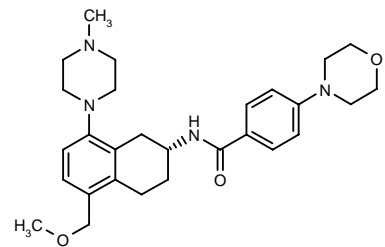
SOURCE – Lundbeck.

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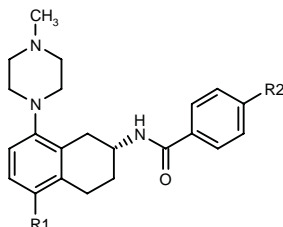
273024

N-[5-(Methoxymethyl)-8-(4-methyl-1-piperazinyl)-1,2,3,4-tetrahydro-2(*R*)-naphthalenyl]-4-(4-morpholinyl)-benzamide



C28 H38 N4 O3; Mol wt: 478.6332

ACTION – Potent and selective, orally bioavailable 5-HT_{1B} receptor antagonist for the treatment of CNS disorders such as depression and anxiety, as well as urinary incontinence, vasospasm and for controlling the growth of tumors. Other specifically claimed substituted 1,2,3,4-tetrahydronaphthalene derivatives include the following:



Compound	R1	R2	Formula
273025	Br	CF ₃	C ₂₃ H ₂₅ BrF ₃ N ₃ O
273026	OH	OBu	C ₂₆ H ₃₅ N ₃ O ₃
273027	OMe	4-morpholinyl-CO	C ₂₈ H ₃₆ N ₄ O ₄
273029	Et	4-morpholinyl	C ₂₈ H ₃₆ N ₄ O ₂
273030	OCHF ₂	4-morpholinyl	C ₂₇ H ₃₄ F ₂ N ₄ O ₃

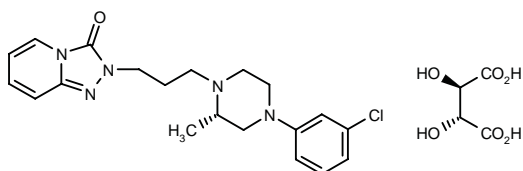
SOURCE – Astra (AstraZeneca).

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1. Berg, S. et al. (Astra AB) *Subst. 1,2,3,4-tetrahydronaphthalene derivs.* WO 9905134.

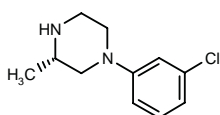
273102^{1,2}

2-[3-[4-(3-chlorophenyl)-2(S)-methylpiperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one L-(+)-tartrate



C₂₀ H₂₄ Cl N₅ O . C₄ H₆ O₆; Mol wt: 535.9820

ACTION – High-affinity ligand for 5-HT_{2A} receptors, an analogue of trazodone with similar affinity for 5-HT_{2A} receptors (IC₅₀ = 25.4 and 17 nM for compound and trazodone, respectively, against [³H]-ketanserin binding in rat cortical membranes) but reduced affinity for α₁-adrenoceptors (IC₅₀ = 981 and 281 nM for compound and trazodone, respectively, against [³H]-prazosin binding in rat cortical membranes). In functional studies, compound antagonized contractions induced by 5-HT in rat aorta and by norepinephrine in rat vas deferens with pA₂ values of 8.5 and 5.4, respectively. Selected for further pharmacological studies as a potential antidepressant. The following compound, a potential metabolite, was also selected for further evaluation:



273167: C₁₁ H₁₅ Cl N₂

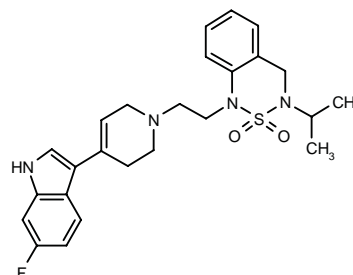
SOURCE – Angelini.

REFERENCES

1. Baiocchi, L. and Cioli, V. (Istituto Ricerca Francesco Angelini SpA) *Pharmacologically active enantiomers.* EP 707587, JP 96512036, WO 9501354.
2. Giannangeli, M. et al. *Effect of modifications of the alkylpiperazine moiety of trazodone on 5HT_{2A} and α₁ receptor binding affinity.* J Med Chem 1999, 42(3): 336.

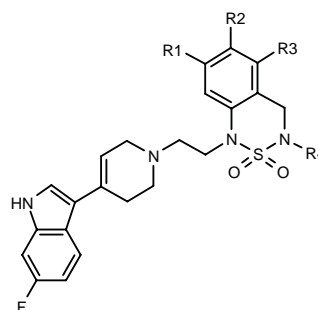
273279

1-[2-[4-(6-Fluoro-1H-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]ethyl]-3-isopropyl-3,4-dihydro-1H-2,1,3-benzothiadiazine-2,2-dioxide



C₂₅ H₂₉ F N₄ O₂ S; Mol wt: 468.5941

ACTION – Agent for the treatment of CNS disorders such as depression, obesity, bulimia, alcoholism, drug addiction, memory loss, Alzheimer's disease, anxiety, schizophrenia and sleep disorders, as well as cardiovascular disorders, gastrointestinal disorders, pain, headache and sexual dysfunction, a combined 5-HT_{2A} antagonist (K_i < 15 nM) and 5-HT reuptake inhibitor. Within this series of benzothiadiazinyl-indole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
273280	H	NH ₂	H	i-Pr	C ₂₅ H ₃₀ FN ₅ O ₂ S
273281	F	H	H	i-Pr	C ₂₅ H ₂₈ F ₂ N ₄ O ₂ S
273282	H	H	F	i-Pr	C ₂₅ H ₂₈ F ₂ N ₄ O ₂ S
273283	H	H	H	H	C ₂₂ H ₂₃ FN ₄ O ₂ S

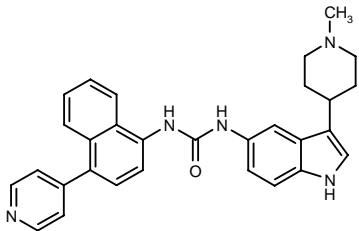
SOURCE – Lilly.

REFERENCES

1. Fairhurst, J. (Eli Lilly and Company, Ltd.) *Benzothiadiazinyl-indole derivs. and their use as serotonin receptor ligands.* EP 897921, JP 99116572, WO 9910346.

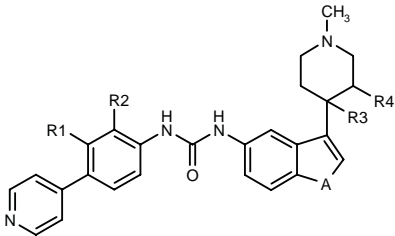
273875

N-[3-(1-Methyl-4-piperidiny)-1*H*-indol-5-yl]-N'-[4-(4-pyridinyl)-1-naphthyl]urea



C30 H29 N5 O; Mol wt: 475.5931

ACTION – Agent for the treatment of CNS disorders such as depression and anxiety with high affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors (pK_i > 8.0 for the three receptor subtypes). Within this series of bicyclic derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	R4	A	Formula
273876	Cl	Cl	H	H	NH	C ₂₆ H ₂₅ Cl ₂ N ₅ O
273877	H	Cl	H	H	NH	C ₂₆ H ₂₆ ClN ₅ O
273878	Cl	H	H	H	NH	C ₂₆ H ₂₆ ClN ₅ O
273879	H	Cl	bond		S	C ₂₆ H ₂₃ ClN ₄ OS
273880	-CH=CHCH=CH-		bond		S	C ₃₀ H ₂₆ N ₄ OS
273881	-CH=CHCH=CH-		H	H	S	C ₃₀ H ₂₈ N ₄ OS

SOURCE – SmithKline Beecham.

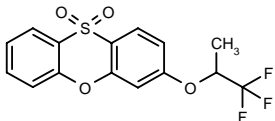
REFERENCES

1. Gaster, L.M. et al. (SmithKline Beecham plc) *Bicyclic cpds. as ligands for 5-HT₁ receptors*. WO 9907700.

2614W94^{1,2}

272849

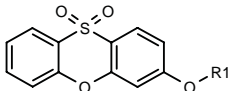
3-[1-(Trifluoromethyl)ethoxy]phenoxathilin-10,10-dioxide



C15 H11 F3 O4 S; Mol wt: 344.3079

ACTION – Potential antidepressant and anxiolytic agent, a potent, selective, competitive and reversible inhibitor of MAO-A (IC₅₀ = 5 nM in rat brain mitochondrial extracts) with no effect against MAO-B at up to 30 nM; K_i values of 1.6 ± 0.2 and 1.1 ± 0.3 nM were obtained using 5-HT and tyramine as substrates, respectively. *Ex vivo* in rats, compound given orally inhibited brain MAO-A with an ID₅₀ of 1.7 mg/kg and maximum inhibition was observed after

0.5 h, indicating rapid transport to the brain; this effect was gradually reversed by 24 h. 2614W94 administered to rats at a dose of 5 mg/kg p.o. induced a significant increase in brain levels of dopamine, 5-HT and norepinephrine, whereas it decreased levels of 5-HT and dopamine metabolites. In behavioral tests in rats, it potentiated head twitches induced by 5-hydroxytryptophan, giving an ED₅₀ of 1.1 mg/kg p.o., whereas it did not potentiate the blood pressure effects caused by dietary tyramine and was not associated with liver toxicity. Two achiral analogues whose activity has not been as extensively studied are:



Compound	R1	Formula
KP9 [272909] ¹⁻³	CH2CF3	C ₁₄ H ₉ F ₃ O ₄ S
1346W95 [272910] ^{1,2}	CH(CHF2)2	C ₁₅ H ₁₀ F ₄ O ₄ S

SOURCE – Krenitsky.

REFERENCES

1. Harfenist, M. et al. (Krenitsky Pharmaceutical, Inc.) *Pharmacologically active cpds. and use*. WO 9812190.

2. White, H.L. et al. *Biochemical and pharmacologic properties of 2614W94, a reversible, competitive inhibitor of monoamine oxidase-A*. Drug Dev Res 1998, 45(1): 1.

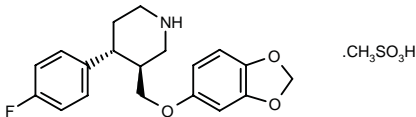
3. *Krenitsky seeks partners to develop MAO-A inhibitors*. DailyDrugNews.com (Daily Essentials) 199 , May 19.

PAROXETINE MESILATE

Rec INNM

273187

(3*S*,4*R*)-3-(1,3-Benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine methanesulfonate



C19 H20 F N O3 . C H4 O3 S; Mol wt: 425.4746

ACTION – Mesylate salt of the antidepressant paroxetine* with improved physicochemical characteristics as compared to known paroxetine salts such as the hydrochloride and the maleate; in particular, compound exhibits lower hygroscopicity than the hydrochloride, much higher stability than the maleate and greatly improved water solubility compared to the hydrochloride hemihydrate and hydrochloride anhydrate forms of paroxetine. A representative compound from a series of sulfonate salts of paroxetine.

SOURCE – Synthon.

REFERENCES

1. Benneker, F.B.G. et al. (Synthon BV) *4-Phenylpiperidine cpds. for treating depression*. US 5874447.

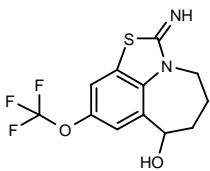
*Drug Data Report 1991, 013(05): 0371.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

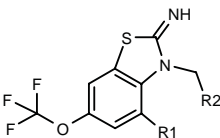
273420

2-Imino-9-(trifluoromethoxy)-4,5,6,7-tetrahydro-2*H*-thiazolo[5,4,3-*jk*][1]benzazepin-7-ol



C12 H11 F3 N2 O2 S; Mol wt: 304.2909

ACTION – Glutamate antagonist and anticonvulsant reported to have an ED₅₀ of 4 mg/kg i.v. or less in the maximal electroshock seizure (MES) assay in mice, compared to an LD₅₀ of at least 15 mg/kg i.v. in this species. Also potentially useful for the treatment of schizophrenia, sleep disorders, anxiety, depression, ischemic disorders, Alzheimer’s disease, Huntington’s disease and Parkinson’s disease. A representative compound from a series of thiazolobenzoheterocyclic derivatives, wherein the following are also specifically claimed:



Compound	R1,R2	Formula
273421	-SO2CH2CH2-	C ₁₁ H ₉ F ₃ N ₂ O ₃ S ₂
273422	-CH2N(CH2Ph)CH2-	C ₁₈ H ₁₆ F ₃ N ₃ OS
273423	-SOCH2CH2-	C ₁₁ H ₉ F ₃ N ₂ O ₂ S ₂
273424	-CH2SC(Me)2-	C ₁₃ H ₁₃ F ₃ N ₂ OS ₂
273425	-CH2SCH(CH2OH)-	C ₁₂ H ₁₁ F ₃ N ₂ O ₂ S ₂

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

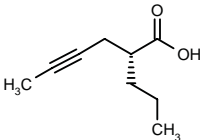
1. Hardy, J.-C. et al. (Rhône-Poulenc Rorer SA) *Thiazolobenzoheterocycles, preparation and medicines containing same*. WO 9905147.

R-ABS-103^{1,4,6}

273087

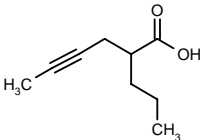
2(*R*)-Propyl-4-hexynoic acid

ABS-103R
R-103



C9 H14 O2; Mol wt: 154.2076

ACTION – Antiepileptic agent, a single isomer of the racemic mixture **ABS-103**, a valproic acid derivative. Compound exhibited equal antiepileptic activity and potency to the racemic mixture but was less toxic and showed no teratogenic potential in animal models.



ABS-103 [215972]¹⁻⁸: C9 H14 O2

SOURCE – American Biogenetic Sciences.

REFERENCES

1. Heinz, N. et al. *VPA-analogous antiepileptics*. DE 4231085, US 5786380, WO 9406743.

2. Heinz, N. et al. *A new analogue of valproic acid with improved anticonvulsant properties and low teratogenic and neurotoxic potential in experimental animals*. Epilepsia 1998, 39(Suppl. 6): Abst 2.040.

3. *ABS patent application for epilepsy drug allowed in Japan*. DailyDrugNews.com (Daily Essentials) 1999, Feb 5.

4. *American Biogenetic Sciences uses chiral technology to produce single isomer version of epilepsy drug ABS-103. R-103 superior in potency and eliminates side effects associated with valproic acid*. American Biogenetic Sciences, Inc. Press Release 1999, Feb 24.

5. *Joint research project will evaluate ABS-103 for the treatment of epilepsy*. DailyDrugNews.com (Daily Essentials) 1998, Aug 13.

6. *Single-isomer version of epilepsy Rx developed at ABS*. DailyDrugNews.com (Daily Essentials) 1999, March 5.

7. American Biogenetic Sciences, Inc. Annual Report 1993.

8. American Biogenetic Sciences, Inc. Annual Report 1994.

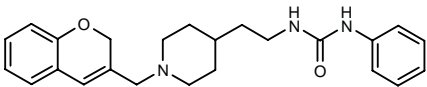
TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

F-10981*

273799

261985 (as hydrochloride)

N-[2-[1-(2*H*-1-Benzopyran-3-ylmethyl)piperidin-4-yl]ethyl]-*N*'-phenylurea



C24 H29 N3 O2; Mol wt: 391.5121

ACTION – Potent α_2 -adrenoceptor antagonist (IC_{50} = 22 nM) with high selectivity over α_1 -adrenoceptors (IC_{50} > 1000 nM) and good selectivity over dopamine D_2 receptors (IC_{50} = 230 nM), as well as good oral bioavailability. *In vivo*, compound antagonized guanabenz-induced hypothermia in mice (ED_{50} = 0.4 mg/kg i.p., 1.8 mg/kg p.o.), and it exhibited potent activity on *d*-amphetamine-induced circling behavior in 6-OHDA-lesioned rats at doses of 2.5-10 mg/kg i.p. Potentially useful for the treatment of neurodegenerative pathologies such as Parkinson's disease.

SOURCE – Pierre Fabre.

REFERENCES

1. Vidaluc, J.-L. et al. (Pierre Fabre Médicament) *Novel benzodioxanes and 1-(2H)-benzopyranes, their preparation and their use as medicine*. WO 9802435.

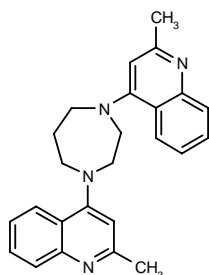
2. Mayer, P. et al. *Modulation of the benzodioxane heterocycle in a novel series of potent α_2 adrenoceptor antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 112.

*Identified compound **261985** (see **261222**) Drug Data Report 1998, 020(05): 0388.

COGNITION-ENHANCING DRUGS

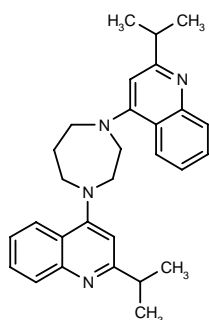
272205

4,4'-(Perhydro-1,4-diazepin-1,4-diyl)bis(2-methyl-quinoline)



C25 H26 N4; Mol wt: 382.5084

ACTION – Agent for the treatment of neurodegenerative disorders, particularly dementia, a potassium channel blocker with high affinity for apamine-sensitive potassium channels. Compound is also reported to be useful for the treatment of depression, mania, myotonic dystrophy, alcoholism, sleep disorders and bronchial asthma. Another specifically claimed compound from this series of ring-bridged bis-quinolines is:



272207: C29 H34 N4

SOURCE – Bayer.

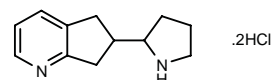
REFERENCES

1. Schohe-Loop, R. et al. (Bayer AG) *Ring-bridged bis-quinolines*. US 5866562.

272528

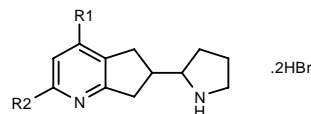
(±)-6-(2-Pyrrolidinyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine dihydrochloride

(±)-6-(2-Pyrrolidinyl)-6,7-dihydro-5*H*-1-pyridine dihydrochloride



C12 H16 N2 . 2HCl; Mol wt: 261.1942

ACTION – Agent with potent and selective affinity for nicotinic acetylcholine receptors, expected to be useful in the treatment of cognitive disorders and other CNS disorders, as well as gastrointestinal disorders. Within this series of 6-pyrrolidin-2-ylpyridine derivatives, the following are also included:



Compound	R1	R2	Formula
272532	Cl	H	C ₁₂ H ₁₅ ClN ₂ .2HBr
272533	H	Cl	C ₁₂ H ₁₅ ClN ₂ .2HBr
272534	H	OMe	C ₁₃ H ₁₈ N ₂ O.2HBr

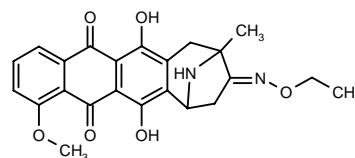
SOURCE – Synthélabo (Sanofi-Synthélabo).

REFERENCES

1. Lochead, A. et al. (Synthélabo) *6-Pyrrolidin-2-ylpyridine derivs., their preparation and application in therapy*. WO 9902517.

272740

6,12-Dihydroxy-7,10-imino-4-methoxy-10-methyl-7,8,9,10,11,13-hexahydro-5*H*-cyclohept[*b*]anthracene-5,9,13-trione 9-(*O*-ethylxime)



C23 H22 N2 O6; Mol wt: 422.4348

ACTION – Agent for the treatment of amyloidosis disorders including neurodegenerative disorders of the Alzheimer's type, with the ability to inhibit the formation of amyloid fibrils *in vitro* (54.2% inhibition at 50 μ M).

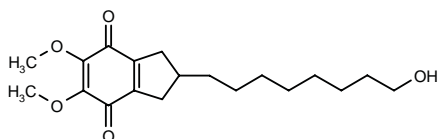
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Caruso, M. et al. (Pharmacia & Upjohn SpA) *Imino-aza-anthracyclinone derivs. for the treatment of amyloidosis*. WO 9832754.

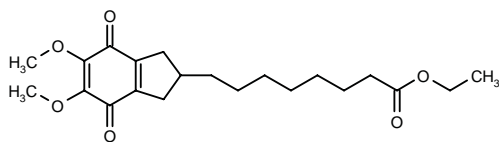
272743

2-(8-Hydroxyoctyl)-5,6-dimethoxy-4,7-dihydroindane-4,7-dione



C19 H28 O5; Mol wt: 336.4252

ACTION – Agent for the treatment of neurodegenerative disorders including Alzheimer's disease and Parkinson's disease, with excellent mitochondrial function-activating activity, as demonstrated by its ability to inhibit peroxylipid formation in rat brain homogenates ($IC_{50} = 0.17\text{--}1.1\ \mu\text{M}$). Another representative compound within this series of bicyclic quinone derivatives is:



272744: C21 H30 O6

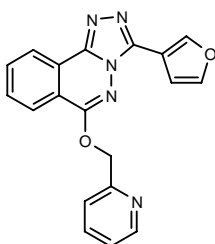
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Bicyclic quinone cpds., their production and use*. JP 98273469, WO 9833758.

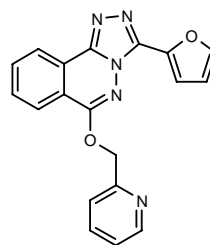
273173

3-(3-Furyl)-6-(2-pyridylmethoxy)[1,2,4]triazolo[3,4-*a*]phthalazine



C19 H13 N5 O2; Mol wt: 343.3447

ACTION – Cognition-enhancing agent acting as a partial or full inverse agonist at the GABA_A $\alpha 5$ binding site, with reduced proconvulsant activity due to its relatively low affinity for $\alpha 1$, $\alpha 2$ and/or $\alpha 3$ binding sites. Another exemplified 1,2,4-triazolo[4,3-*b*]pyridazine derivative is:



273174: C19 H13 N5 O2

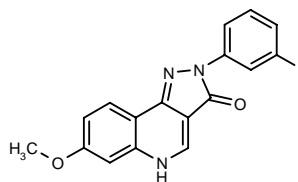
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Therapeutically active 1,2,4-triazolo(4,3-*b*) pyridazine derivs. as ligands for GABA receptors*. WO 9906407.

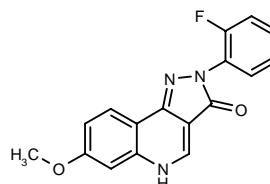
273179

2-(3-Fluorophenyl)-7-methoxy-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-3-one



C17 H12 F N3 O2; Mol wt: 309.2988

ACTION – Cognition-enhancing agent with partial or full inverse agonist activity at the GABA_A $\alpha 5$ binding site and reduced proconvulsant activity due to its relatively low affinity for $\alpha 1$, $\alpha 2$ and/or $\alpha 3$ binding sites. Another specifically claimed pyrazoloquinolinone derivative is:



273180: C17 H12 F N3 O2

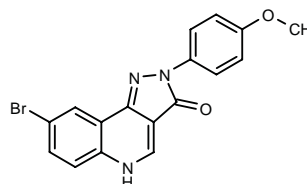
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Bourrain, S. et al. (Merck Sharp & Dohme Ltd.) *Pyrazoloquinolinone derivs. as GABA $\alpha 5$ receptor inverse agonists*. WO 9906400.

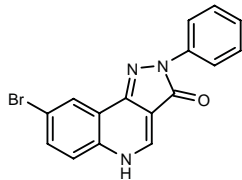
273184

8-Bromo-2-(4-methoxyphenyl)-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-3-one



C17 H12 Br N3 O2; Mol wt: 370.2048

ACTION – Cognition-enhancing agent with partial or full inverse agonist activity at GABA_A α5 binding sites and reduced proconvulsant activity due to its relatively low affinity for α1, α2 and/or α3 binding sites. Another specifically claimed aryl-substituted pyrazoloquinolinone derivative is:



273185: C16 H10 Br N3 O

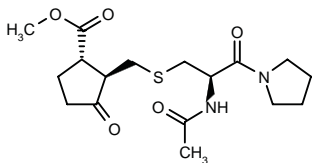
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Bourrain, S. et al. (Merck Sharp & Dohme Ltd.) *Aryl-substd. pyrazoloquinolinone derivs. as GABA α5 receptor inverse agonists.* WO 9906399.

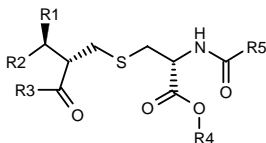
273440

trans-2-[2(*R*)-(Acetamido)-3-oxo-3-(1-pyrrolidiny)-propylsulfanylmethyl]-3-oxocyclopentanecarboxylic acid methyl ester

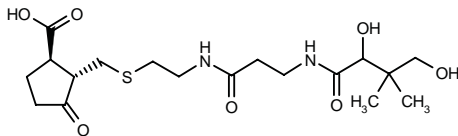


C17 H26 N2 O5 S; Mol wt: 370.4674

ACTION – Agent for the treatment of CNS disorders and peripheral nerve disorders by virtue of its ability to promote neuronal differentiation, as demonstrated in PC12 cell cultures, where it exhibited a minimum effective dose (MED) of 0.8 µg/ml for inducing axonal outgrowth. Other related compounds include the following:



Compound	R1	R2,R3	R4	R5	Isomer	Formula
273443	CO2Et	-CH2-	Me	Me	trans	C ₁₄ H ₂₁ NO ₆ S
273444	CH2OH	-(CH2)2-	H	CF2CF3	trans	C ₁₃ H ₁₆ F ₅ NO ₅ S



273442: C18 H30 N2 O7 S

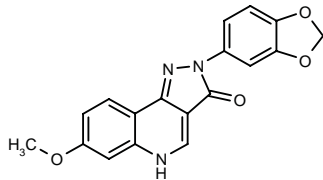
SOURCE – Nippon Kayaku.

REFERENCES

1. Saito, S. et al. (Nippon Kayaku Co., Ltd.) *Novel cpd. having effect of promoting neuron differentiation.* JP 99049718, JP 99100344, WO 9905091.

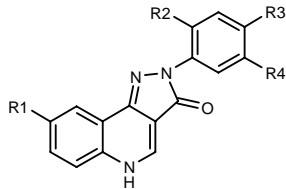
273515

2-(1,3-Benzodioxol-5-yl)-7-methoxy-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-3-one



C18 H13 N3 O4; Mol wt: 335.3177

ACTION – Cognition-enhancing agent particularly for the treatment of Alzheimer’s disease, a selective inverse agonist at GABA_A α5 receptors; it is expected to be free from proconvulsant activity by virtue of its selectivity relative to α1, α2 and/or α3 receptor binding sites. Within this series of 2-aryl-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-3-one derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
273516	H	H	-OCH2O-		C ₁₇ H ₁₁ N ₃ O ₃
273517	H	F	H	F	C ₁₆ H ₉ F ₂ N ₃ O
273518	F	H	-OCH2O-		C ₁₇ H ₁₀ FN ₃ O ₃
273519	F	F	H	F	C ₁₆ H ₈ F ₃ N ₃ O
273520	Cl	F	H	F	C ₁₆ H ₈ ClF ₂ N ₃ O
273521	Me	F	H	F	C ₁₇ H ₁₁ F ₂ N ₃ O
273522	OMe	H	OMe	F	C ₁₈ H ₁₄ FN ₃ O ₃
273523	ethynyl-CH2N(Me)2	F	H	F	C ₂₁ H ₁₆ F ₂ N ₄ O
273524	F	H	OEt	H	C ₁₈ H ₁₄ FN ₃ O ₂
273525	Me	H	OMe	F	C ₁₈ H ₁₄ FN ₃ O ₂
273526	F	H	OMe	F	C ₁₇ H ₁₁ F ₂ N ₃ O ₂

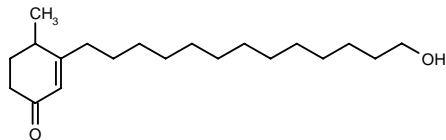
SOURCE – Merck Sharp & Dohme.

REFERENCES

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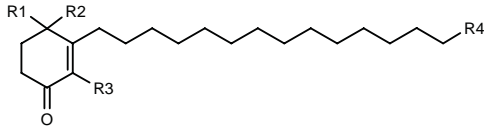
274019

3-(13-Hydroxytridecyl)-4-methyl-2-cyclohexen-1-one



C20 H36 O2; Mol wt: 308.5024

ACTION – Agent for the treatment or prevention of Alzheimer's disease by virtue of its ability to potently stimulate neurite growth (> 200% at 50 nM in cultures of fetal rat brain neurons) and which is reported to cross the blood–brain barrier. A representative compound from a series of long-chain alcohol derivatives of 2-cyclohexen-1-one, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
274020	Me	H	H	OH	C ₂₁ H ₃₈ O ₂
274021	H	H	Me	OH	C ₂₁ H ₃₈ O ₂
274022	Me	Me	Me	OH	C ₂₃ H ₄₂ O ₂
274023	Me	Me	Me	CH ₂ OH	C ₂₄ H ₄₄ O ₂

SOURCE – Meiji Milk Products.

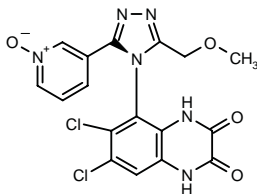
REFERENCES

1. Luu, B. et al. (Meiji Milk Products Co., Ltd.) *Cyclohexenone long-chain alcohol and medicament containing same*. WO 9908987.

TREATMENT OF CEREBROVASCULAR DISEASES

272737

(–)-6,7-Dichloro-5-[3-(methoxymethyl)-5-(1-oxidopyridin-3-yl)-4*H*-1,2,4-triazol-4-yl]quinoxaline-2,3-(1*H*,4*H*)-dione



C17 H12 Cl2 N6 O4; Mol wt: 435.2258

ACTION – Agent for the treatment of neurodegenerative disorders, a quinoxalinedione derivative with antagonist activity at the glycine site of the NMDA receptor (IC₅₀ = 2.4 nM) and very low affinity for the AMPA receptor; it also demonstrated functional *in vitro* glycine antagonism (IC₅₀ = 140 nM).

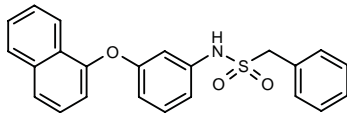
SOURCE – Pfizer.

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1. Stobie, A. et al. (Pfizer Ltd.;Pfizer Inc.) *Quinoxalinediones*. WO 9838186.

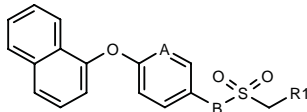
273058

N-[3-(1-Naphthalenyloxy)phenyl]benzylsulfonamide



C23 H19 N O3 S; Mol wt: 389.4731

ACTION – Agent for the treatment of neurodegenerative disorders, particularly stroke and craniocerebral trauma, with affinity for rat CB₁ cannabinoid receptors (IC₅₀ = 0.9 nM) and for human CB₂ receptors (K_i = 41 nM). Compound was active *in vivo* in a model of cerebral ischemia in rats, giving a 24% reduction in infarct volume at a dose of 0.1 mg/kg i.v. and a 54% reduction in subdural hematoma at a dose of 0.01 mg/kg/h. Within this series of aryl sulfonamide derivatives, the following are also included:



Compound	R1	A	B	Formula
273059	Pr	CH	NH	C ₂₀ H ₂₁ NO ₃ S
273060	Ph	N	NH	C ₂₂ H ₁₈ N ₂ O ₃ S
273061	CH ₂ CH ₂ Cl	CH	NH	C ₁₉ H ₁₈ ClNO ₃ S
273062	Pr	CH	O	C ₂₀ H ₂₀ O ₄ S

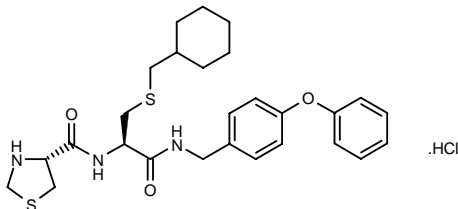
SOURCE – Bayer.

REFERENCES

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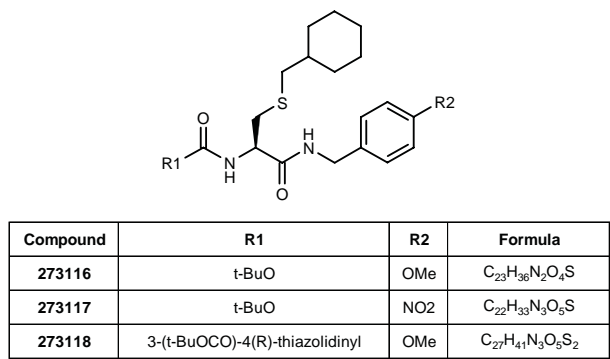
273115

S-(Cyclohexylmethyl)-*N*-[thiazolidin-4(*R*)-ylcarbonyl]-*L*-cysteine 4-phenoxybenzylamide hydrochloride



C27 H35 N3 O3 S2 . HCl; Mol wt: 550.1844

ACTION – Cerebral antiischemic agent with N-type calcium channel-antagonist activity. Within this series of amino acid derivatives, the following are also included:



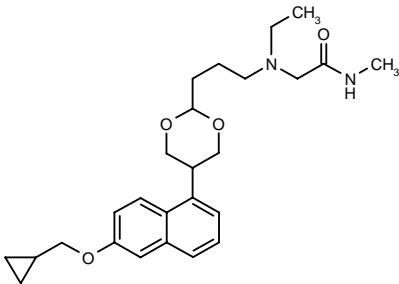
SOURCE – Ono.

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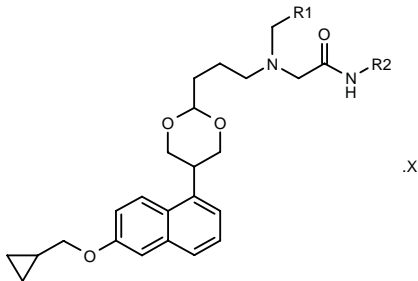
273350

2-[N-[3-[5-[6-(Cyclopropylmethoxy)-1-naphthyl]-1,3-dioxan-2-yl]propyl]-N-ethylamino]-N-methylacetamide



C26 H36 N2 O4; Mol wt: 440.5804

ACTION – Cerebral antiischemic, anticonvulsant, neuroprotective and antinociceptive agent, a representative compound from a series of substituted 5-naphthyl-1,3-dioxane derivatives acting as neuronal sodium channel antagonists, wherein the following are also included:



Compound	R1	R2	X	Formula
273352	Me	cyclopropyl-CH2	HCl	C ₂₉ H ₄₀ N ₂ O ₄ .HCl
273353	Me	cyclopropyl		C ₂₈ H ₃₈ N ₂ O ₄
273354	cyclopropyl	H	HCl	C ₂₇ H ₃₆ N ₂ O ₄ .HCl
273355	cyclopropyl	Me	HCl	C ₂₈ H ₃₈ N ₂ O ₄ .HCl
273356	cyclopropyl	cyclopropyl-CH2		C ₃₁ H ₄₂ N ₂ O ₄

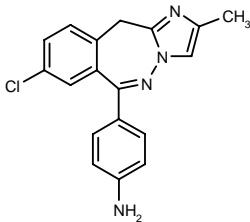
SOURCE – Synthélabo (Sanofi-Synthélabo).

REFERENCES

1. Dargazanli, G. et al. (Synthélabo) *5-Naphthalen-1-yl-1,3-dioxane derivs., preparation and therapeutic application.* WO 9855474.

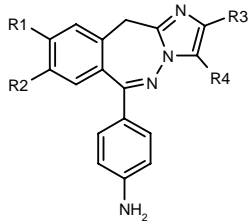
273541

4-(8-Chloro-2-methyl-11 *H*-imidazo[1,2-*c*][2,3]benzo-diazepin-6-yl)phenylamine



C18 H15 Cl N4; Mol wt: 322.7975

ACTION – Neuroprotective, anticonvulsant and cerebral antiischemic agent, an excitatory amino acid receptor antagonist that acts at AMPA and kainate receptors (IC₅₀ = 2.02 and 4.97 μM for inhibition of AMPA- and kainate-induced currents in Purkinje cells). Compound is active in the maximal electroshock seizure assay (ED₅₀ = 24 mg/kg p.o.) and against convulsions induced by several chemical agents (ED₅₀ = 13-67 mg/kg p.o.) in mice. Muscle relaxant activity was shown in the rotarod test in mice (ED₅₀ = 16 mg/kg i.p.). Neuroprotection was demonstrated in a rat model of focal ischemia induced by middle cerebral artery occlusion, where it reduced infarct area by 60.2% at 6 mg/kg i.v. Within this series of 2,3-benzodiazepine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
273542	H	Cl	H	Me	C ₁₈ H ₁₅ ClN ₄
273543	H	Br	Me	H	C ₁₈ H ₁₅ BrN ₄
273544	Cl	Cl	Me	H	C ₁₈ H ₁₄ Cl ₂ N ₄

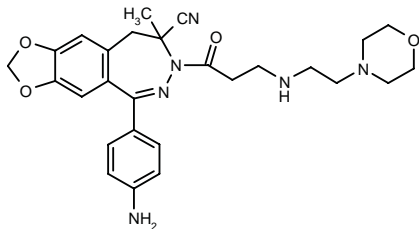
SOURCE – Gyogyszerkutato Intezet.

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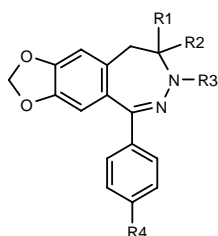
273864

(±)-5-(4-Aminophenyl)-8-methyl-7-[3-[2-(4-morpholinyl)-ethylamino]propionyl]-8,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]-[2,3]benzodiazepine-8-carbonitrile



C27 H32 N6 O4; Mol wt: 504.5878

ACTION – An AMPA/kainate receptor antagonist with potential as a muscle relaxant, neuroprotective and anti-convulsant. AMPA-antagonist activity was demonstrated *in vitro* in the quisqualate neurotoxicity test, in the population spike test and in the spreading depression test (IC_{50} = 5.4, 3.0 and 3.7 μ M, respectively). Muscle relaxant activity was tested in mice following i.p. administration (ED_{50} = 31.3 mg/kg i.p.). Anticonvulsant effects were measured in mice in the maximal electroshock seizure (MES) test (ED_{50} = 2.3 mg/kg i.p.), as well as in the audiogenic seizure test, where it inhibited both clonic seizures and tonic extensor convulsions (ED_{50} = 5.4 and 1.2 mg/kg i.p., respectively). Neuroprotective activity was demonstrated in the magnesium chloride-induced global ischemia test in mice (ID_{50} = 7 mg/kg i.p.). LD_{50} was about 300 mg/kg i.p. and > 500 mg/kg p.o. in mice. A representative compound from a series of 8-substituted-9H-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
273865	CN	Me	COCH ₂ Cl	NO ₂	C ₂₀ H ₁₅ ClN ₄ O ₅
273866	CONH ₂		bond	NH ₂	C ₁₇ H ₁₄ N ₄ O ₃
273867	CN		bond	NH ₂	C ₁₇ H ₁₂ N ₄ O ₂

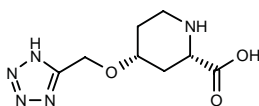
SOURCE – Egis.

REFERENCES

1. Rátkai, Z. et al. (Egis Pharmaceuticals Ltd.) 8-Subst.-9H-1,3-dioxolo[4,5-*h*][2,3]-benzodiazepine derivs., as AMPA/kainate receptor inhibitors. WO 9907707.

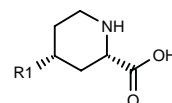
273988

(2*R**,4*S**)-4-(1*H*-Tetrazol-5-ylmethoxy)piperidine-2-carboxylic acid

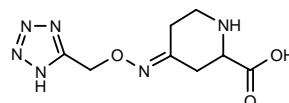


C₈ H₁₃ N₅ O₃; Mol wt: 227.2227

ACTION – Neuroprotective agent, a selective NMDA receptor antagonist with poor affinity for AMPA and kainate receptors. Claimed for the treatment of epilepsy, stroke, anxiety, cerebral ischemia and muscle spasms. A representative compound from a series of piperidine tetrazole derivatives, wherein the following are also included:



Compound	R1	Formula
273989	5-tetrazolyl-CH ₂ OCH ₂	C ₉ H ₁₅ N ₅ O ₃
273992	5-tetrazolyl-S	C ₇ H ₁₁ N ₅ O ₂ S
273993	5-SH-1-tetrazolyl	C ₇ H ₁₁ N ₅ O ₂ S
273994	5-SH-2-tetrazolyl	C ₇ H ₁₁ N ₅ O ₂ S



273990: C₈ H₁₂ N₆ O₃

SOURCE – Lilly.

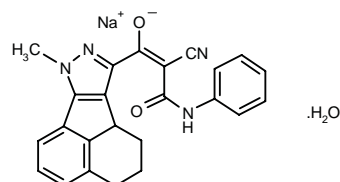
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PNU-155154A

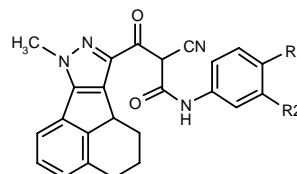
273585

2-Cyano-3-hydroxy-3-(7-methyl-2,3,7,9b-tetrahydro-1*H*-acenaphtho[1,2-*c*]pyrazol-9-yl)-*N*-phenyl-2-propenamide sodium salt hydrate

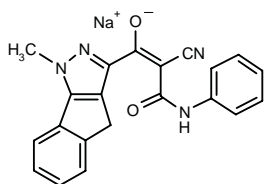


C₂₄ H₁₉ N₄ Na O₂ . H₂O; Mol wt: 436.4449

ACTION – Neuroprotective agent that inhibits the enzyme kynurenine 3-hydroxylase (kynurenine 3-monooxygenase; IC_{50} = 0.14 μ M), a major enzyme in the metabolic pathway of kynurenine. Within this series of specifically claimed condensed pyrazole derivatives, the following are also included:



Compound	R1	R2	Formula
PNU-151567 [273586]	OMe	H	C ₂₅ H ₂₂ N ₄ O ₃
PNU-152633 [273587]	H	NO ₂	C ₂₄ H ₁₉ N ₅ O ₄
PNU-151527 [273588]	H	Me	C ₂₅ H ₂₂ N ₄ O ₂



PNU-168755A [273589]: C₂₁ H₁₅ N₄ Na O₂

SOURCE – Pharmacia & Upjohn.

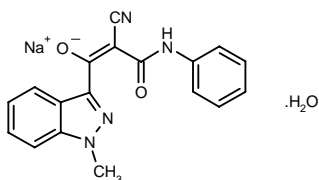
REFERENCES

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PNU-168704A

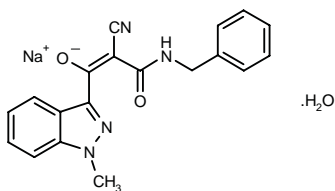
273176

2-Cyano-3-hydroxy-3-(1-methyl-1H-indazol-3-yl)-N-phenyl-2-propanamide sodium salt hydrate



C₁₈ H₁₃ N₄ Na O₂ · H₂O; Mol wt: 358.3315

ACTION – Neuroprotective agent that acts through inhibition of kynurenine 3-hydroxylase (kynurenine 3-monooxygenase; IC₅₀ = 1.1 μM), a major enzyme in the metabolic pathway of kynurenine. Another fused heterocyclic compound is:



PNU-190349A [273177]: C₁₉ H₁₅ N₄ Na O₂ · H₂O

SOURCE – Pharmacia & Upjohn.

REFERENCES

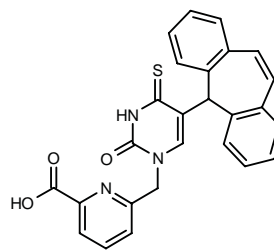
1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *Fused heterocyclic cpds. and their use as kynurenine-3-hydroxylase inhibitors.* WO 9906375.

RESPIRATORY DRUGS

ASTHMA THERAPY

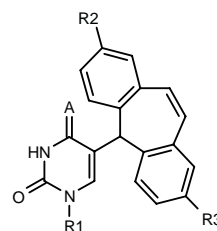
272520

6-[5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-2-oxo-4-thioxo-1,2,3,4-tetrahydro-1-pyrimidinylmethyl]-2-pyridinecarboxylic acid



C₂₆ H₁₉ N₃ O₃ S; Mol wt: 453.5201

ACTION – P2Y₂ receptor antagonist (pA₂ > 4.0 in Jurkat cells transfected with human receptors) potentially useful in the treatment of inflammatory disorders such as asthma, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, rheumatoid arthritis, myocardial ischemia, chronic obstructive pulmonary disease (COPD), cystic fibrosis, atherosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke, as well as cancer. Within this series of specifically claimed compounds, the following are also included:

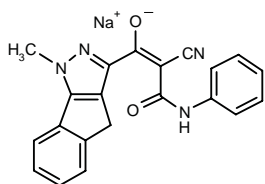


Compound	R1	R2	R3	A	Formula
272521	5-CF ₃ -1,2,4-triazol-3-yl-S	H	H	S	C ₂₂ H ₁₄ F ₃ N ₅ OS ₂
272522	2-(CO ₂ HCH ₂ NH)-4-Pyr	H	H	S	C ₂₆ H ₂₀ N ₄ O ₃ S
272523	2-(4-CO ₂ H-2-thienyl-NHCOCH ₂ NH)-4-Pyr	Me	Et	O	C ₃₄ H ₂₉ N ₅ O ₅ S
272526	4-(CO ₂ HCH ₂ NH)-5-(CO ₂ Me)-2-pyrimidinyl	Me	Me	O	C ₂₉ H ₂₅ N ₅ O ₆
272527	2-[4-(CH ₂ CO ₂ H)-2-thiazolyl-NHCOCH ₂ N(Me)]-4-pyrimidinyl	Et	Me	O	C ₃₄ H ₃₁ N ₇ O ₅ S

SOURCE – Astra (AstraZeneca).

REFERENCES

1. Kindon, N. et al. (Astra Pharmaceuticals Ltd.; Astra AB) *Novel cpds.* WO 9902501.



PNU-168755A [273589]: C₂₁ H₁₅ N₄ Na O₂

SOURCE – Pharmacia & Upjohn.

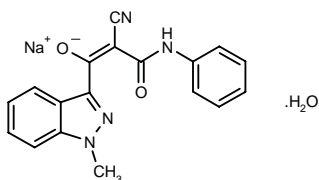
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PNU-168704A

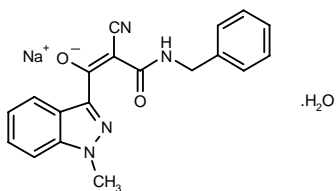
273176

2-Cyano-3-hydroxy-3-(1-methyl-1H-indazol-3-yl)-N-phenyl-2-propenamide sodium salt hydrate



C₁₈ H₁₃ N₄ Na O₂ · H₂O; Mol wt: 358.3315

ACTION – Neuroprotective agent that acts through inhibition of kynurenine 3-hydroxylase (kynurenine 3-monooxygenase; IC₅₀ = 1.1 μM), a major enzyme in the metabolic pathway of kynurenine. Another fused heterocyclic compound is:



PNU-190349A [273177]: C₁₉ H₁₅ N₄ Na O₂ · H₂O

SOURCE – Pharmacia & Upjohn.

REFERENCES

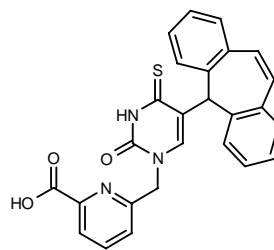
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RESPIRATORY DRUGS

ASTHMA THERAPY

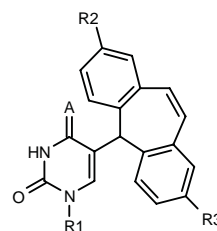
272520

6-[5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-2-oxo-4-thioxo-1,2,3,4-tetrahydro-1-pyrimidinylmethyl]-2-pyridinecarboxylic acid



C₂₆ H₁₉ N₃ O₃ S; Mol wt: 453.5201

ACTION – P2Y₂ receptor antagonist (pA₂ > 4.0 in Jurkat cells transfected with human receptors) potentially useful in the treatment of inflammatory disorders such as asthma, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, rheumatoid arthritis, myocardial ischemia, chronic obstructive pulmonary disease (COPD), cystic fibrosis, atherosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke, as well as cancer. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	R3	A	Formula
272521	5-CF ₃ -1,2,4-triazol-3-yl-S	H	H	S	C ₂₂ H ₁₄ F ₃ N ₅ OS ₂
272522	2-(CO ₂ HCH ₂ NH)-4-Pyr	H	H	S	C ₂₆ H ₂₀ N ₄ O ₃ S
272523	2-(4-CO ₂ H-2-thienyl-NHCOCH ₂ NH)-4-Pyr	Me	Et	O	C ₃₄ H ₂₉ N ₅ O ₅ S
272526	4-(CO ₂ HCH ₂ NH)-5-(CO ₂ Me)-2-pyrimidinyl	Me	Me	O	C ₂₉ H ₂₅ N ₅ O ₆
272527	2-[4-(CH ₂ CO ₂ H)-2-thiazolyl-NHCOCH ₂ N(Me)]-4-pyrimidinyl	Et	Me	O	C ₃₄ H ₃₁ N ₇ O ₅ S

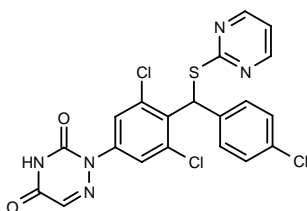
SOURCE – Astra (AstraZeneca).

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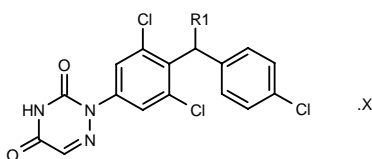
272556

2-[3,5-Dichloro-4-[1-(4-chlorophenyl)-1-(2-pyrimidinyl-sulfanyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione



C20 H12 Cl3 N5 O2 S; Mol wt: 492.7728

ACTION – Agent for the treatment of eosinophil-dependent inflammatory diseases such as bronchial asthma and allergic diseases, an IL-5 inhibitor providing marked inhibition of IL-5 production in human whole blood stimulated by phytohemagglutinin at a concentration of 2 µg/ml. Other particularly preferred 6-azauracil derivatives include the following:



Compound	R1	X	Formula
272557	2-(4-Pyr)-4-thiazolyl	HCl H2O	C ₂₄ H ₁₄ Cl ₃ N ₅ O ₂ S .HCl.H ₂ O
272558	5-Ph-1,3,4-oxadiazol-2-yl		C ₂₄ H ₁₄ Cl ₃ N ₅ O ₃
272559	4-(2-Cl-Ph)-2-thiazolyl		C ₂₅ H ₁₄ Cl ₄ N ₄ O ₂ S
272560	4-(3-F-Ph)-2-thiazolyl		C ₂₅ H ₁₄ Cl ₃ FN ₄ O ₂ S
272561	2-Pyr-S		C ₂₁ H ₁₃ Cl ₃ N ₄ O ₂ S

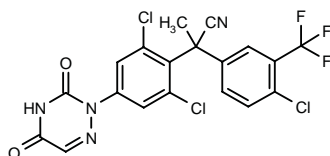
SOURCE – Janssen.

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1. Lacrampe, J.F.A. et al. (Janssen Pharmaceutica NV) *IL-5 inhibiting 6-azauracil derivs.* WO 9902505.

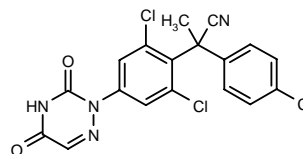
272562

(±)-2-[4-Chloro-3-(trifluoromethyl)phenyl]-2-[2,6-dichloro-4-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)-phenyl]propionitrile



C19 H10 Cl3 F3 N4 O2; Mol wt: 489.6670

ACTION – Agent for the treatment of eosinophil-dependent inflammatory diseases such as asthma and allergic diseases, an inhibitor of the production of the cytokine IL-5, as demonstrated *in vitro* in human whole blood stimulated by phytohemagglutinin (95% inhibition at 2 µg/ml). Another particularly potent inhibitor of IL-5 formation within this series of 6-azauracil derivatives is:



272563: C18 H11 Cl3 N4 O2

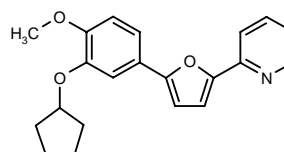
SOURCE – Janssen.

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1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) *6-Azauracil derivs. as IL-5 inhibitors.* WO 9902504.

272669

2-[5-[3-Cyclopentyloxy-4-methoxyphenyl]furan-2-yl]-pyridine



C21 H21 N O3; Mol wt: 335.4009

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with an IC₅₀ of 24 nM against human recombinant enzyme; it was at least 6-fold less potent than rolipram, but it was also 30-fold less emetic (threshold dose of 10 mg/kg p.o. in ferrets). Potentially useful for the treatment of bronchial asthma.

SOURCE – Merck Frosst.

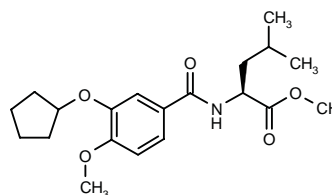
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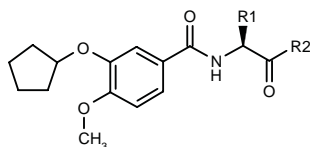
273079

N-[3-(Cyclopentyloxy)-4-methoxybenzoyl]-L-leucine methyl ester



C20 H29 N O5; Mol wt: 363.4511

ACTION – Agent for the treatment of inflammatory disorders, particularly bronchial asthma, allergic rhinitis and arthritis, an inhibitor of phosphodiesterase type 4 (PDE4), producing 77% inhibition of partially purified enzyme from human U937 cells at a concentration of 1 µM vs. 59.7% inhibition for rolipram at the same concentration. Also reported to inhibit tumor necrosis factor (TNF). Other specifically claimed catechol amino acid derivatives include the following:



Compound	R1	R2	Formula
273081	CH ₂ Ph	OEt	C ₂₄ H ₂₉ NO ₅
273082	CH ₂ Ph	NH ₂	C ₂₂ H ₂₆ N ₂ O ₄
273086	H	OEt	C ₁₇ H ₂₃ NO ₅

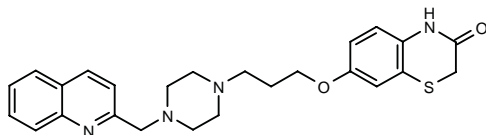
SOURCE – Cheil Jedang.

REFERENCES

1. Rhee, C.K. et al. (Cheil Jedang Corporation) *Catechol amino acid derivs. and pharmaceutical compsns. containing them.* WO 9856756.

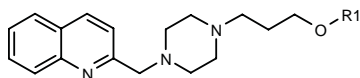
273492

7-[3-[4-(2-Quinolinylmethyl)-1-piperazinyl]propoxy]-3,4-dihydro-2H-1,4-benzothiazin-3-one



C₂₅ H₂₈ N₄ O₂ S; Mol wt: 448.5882

ACTION – Antiasthmatic agent with histamine-antagonist activity, as demonstrated in functional assays by inhibition of histamine-induced guinea pig ileum contractions ($pA_2 = 10.06$ vs. 8.24 for terfenadine) and in binding assays by inhibition of [³H]-mepyramine binding to H₁ receptors in guinea pig brain preparations ($K_D = 5.01$ nM vs. 152 nM for terfenadine). In addition, compound exhibited weak LTD₄ (CysLT₁) receptor-antagonist activity ($K_D = 9.41$ μ M). When tested *ex vivo* in mice, it inhibited [³H]-mepyramine binding with an ID₅₀ value of 8.5 mg/kg i.p. compared to a value of 26 mg/kg i.p. for terfenadine, while showing reduced brain penetration. Other compounds from this series of piperazine derivatives include the following:



Compound	R1	Formula
273493	8-Me-2-oxo-1,2,3,4-tetrahydro-5-quinoliny	C ₂₇ H ₃₂ N ₄ O ₂
273494	3,3,7-(Me)3-2-oxo-4-indoliny	C ₂₈ H ₃₄ N ₄ O ₂
273495	3,3-(Me)2-2-oxo-7-indoliny	C ₂₇ H ₃₂ N ₄ O ₂
273497	2-oxo-1,2-dihydro-7-quinoliny	C ₂₆ H ₂₈ N ₄ O ₂

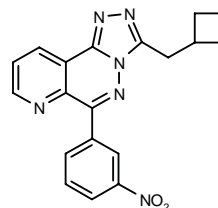
SOURCE – Kowa.

REFERENCES

1. Timmerman, H. et al. (Kowa Co., Ltd.) *Diamine derivs. and pharmaceutical containing the same.* WO 9902520.

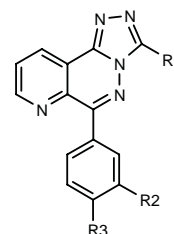
273527

3-(Cyclobutylmethyl)-6-(3-nitrophenyl)pyrido[3,2-*d*][1,2,4]-triazolo[4,3-*b*]pyridazine



C₁₉ H₁₆ N₆ O₂; Mol wt: 360.3754

ACTION – Potent inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.2 μ M against guinea pig ventricular PDE4) with potential in the treatment of allergic, inflammatory and immunological disorders. A representative compound from a series of pyrido[3,2-*d*]-[1,2,4]triazolo[4,3-*b*]pyridazines, wherein the following are also included:



Compound	R1	R2	R3	Formula
273528	i-Bu	H	H	C ₁₈ H ₁₇ N ₅
273529	i-Bu	H	F	C ₁₈ H ₁₆ FN ₅
273530	cyclopentyl-CH ₂	F	H	C ₂₀ H ₁₈ FN ₅
273531	i-Bu	Cl	H	C ₁₈ H ₁₆ ClN ₅
273532	cyclopropyl-CH ₂	Cl	H	C ₁₈ H ₁₄ ClN ₅
273533	cyclopropyl-CH ₂	NO ₂	H	C ₁₈ H ₁₄ N ₆ O ₂
273534	cyclobutyl-CH ₂	NO ₂	H	C ₁₉ H ₁₆ N ₆ O ₂
275629	cyclopropyl	H	H	C ₁₇ H ₁₃ N ₅

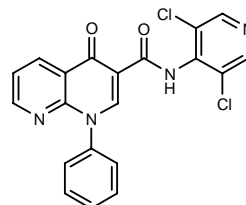
SOURCE – Almirall Prodesfarma.

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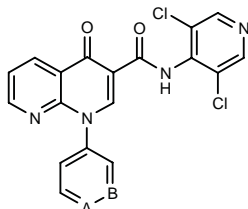
273816

N-(3,5-Dichloro-4-pyridinyl)-4-oxo-1-phenyl-1,4-dihydro-[1,8]naphthyridine-3-carboxamide



C₂₀ H₁₂ Cl₂ N₄ O₂; Mol wt: 411.2468

ACTION – Agent for the treatment of respiratory, CNS and inflammatory disorders, sepsis, Crohn's disease and AIDS, a selective inhibitor of phosphodiesterase type 4 (PDE4; IC_{50} = 0.2 nM) and the production of tumor necrosis factor (TNF- α ; IC_{50} = 0.4 nM in lipopolysaccharide-stimulated murine macrophages). Other compounds from this series of 1-aryl-1,8-naphthyridin-4-one derivatives include the following:



Compound	A	B	Formula
273817	CF	CH	$C_{20}H_{11}Cl_2FN_4O_2$
273818	C(OMe)	CH	$C_{21}H_{14}Cl_2N_4O_3$
273819	CCl	CH	$C_{20}H_{11}Cl_3N_4O_2$
273820	CH	N	$C_{19}H_{11}Cl_2N_5O_2$
273821	N	CH	$C_{19}H_{11}Cl_2N_5O_2$

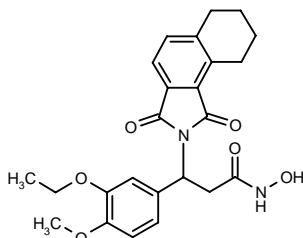
SOURCE – Suntory.

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1. Shimamoto, T. et al. (Suntory Ltd.) 1-Aryl-1,8-naphthyridin-4-one deriv. as type IV phosphodiesterase inhibitor. JP 99106385, WO 9907704.

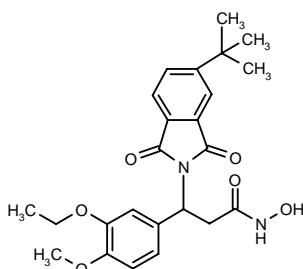
273913

3-(1,3-Dioxo-1,3,6,7,8,9-hexahydro-2H-benzo[e]isoindol-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanohydroxamic acid



C24 H26 N2 O6; Mol wt: 438.4774

ACTION – Potent phosphodiesterase type 4 (PDE4) inhibitor with an IC_{50} of 0.042 nM; it also inhibits lipopolysaccharide (LPS)-stimulated tumor necrosis factor (TNF- α) release from both human peripheral blood mononuclear cells (PBMNs; IC_{50} = 130 nM) and rat whole blood (IC_{50} = 97 nM). Compound interacts with the high-affinity rolipram binding site with an IC_{50} of 3.6 nM. Potentially useful as an antiinflammatory agent, especially for the therapy of bronchial asthma. Another related *N*-phthaloyl- β -aryl- β -amino derivative is:



273912: C24 H28 N2 O6

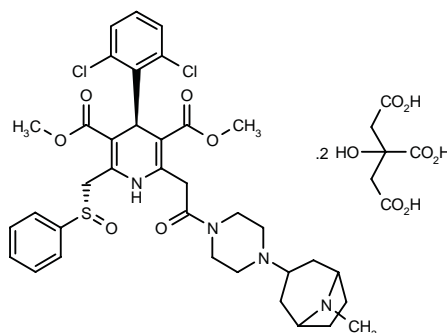
SOURCE – Celgene.

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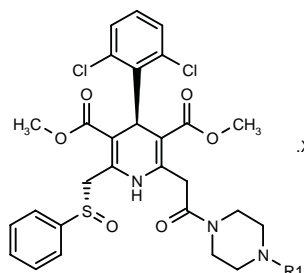
273976

(-)-4(S)-(2,6-Dichlorophenyl)-2-[2-[4-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-piperazinyl]-2-oxoethyl]-6-[(S)-phenylsulfinylmethyl]-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester dicitrate

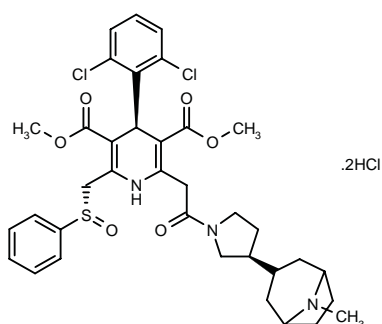


C36 H42 Cl2 N4 O6 S . 2 C6 H8 O7; Mol wt: 1113.9660

ACTION – Bradykinin B_2 receptor antagonist (IC_{50} < 50 nM) with potential in the treatment of inflammation, cardiovascular disease, pain, the common cold, allergies, asthma, pancreatitis, burns, viral infections, head injury, Alzheimer's disease and multiple trauma. Other specifically claimed compounds from this series of optically active 1,4-dihydropyridine derivatives include the following:



Compound	R1	X	Formula
273978	8-Ac-8-azabicyclo-[3.2.1]oct-3-yl	HCl	$C_{37}H_{42}Cl_2N_4O_7S$.HCl
273979	8-Et-8-azabicyclo-[3.2.1]oct-3-yl	2HCl	$C_{37}H_{44}Cl_2N_4O_6S$.2HCl
273981	7-oxobicyclo-[3.3.0]oct-3-yl	citrate	$C_{36}H_{36}Cl_2N_3O_7S$.C ₆ H ₈ O ₇
273982	1-pyrrolidinyl- -COCH ₂ CH ₂	HCl	$C_{35}H_{40}Cl_2N_4O_7S$.HCl
273984	2-oxo-1-pyrrolidinyl- -(CH ₂) ₃	HCl	$C_{35}H_{40}Cl_2N_4O_7S$.HCl
273985	3-Ac-3-azabicyclo-[3.3.0]oct-7-yl	HCl	$C_{37}H_{42}Cl_2N_4O_7S$.HCl



273980: C36 H41 Cl3 N3 O6 S . 2HCl

SOURCE – Pfizer.

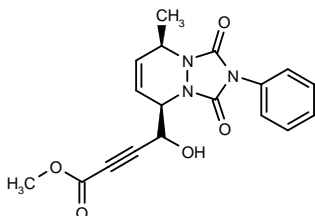
REFERENCES

1. Ikeda, T. et al. (Pfizer Inc.) *Optical active 1,4-dihydropyridine cpds. as bradykinin antagonists*. EP 899261, JP 99106375.

MOL-294

273905

cis-4-Hydroxy-4-(8-methyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-5-yl)-2-butynoic acid methyl ester



C₁₈ H₁₇ N₃ O₅; Mol wt: 355.3483

ACTION – Potent, small-molecule inhibitor of NF- κ B proven to block the NF- κ B-dependent activation of cell adhesion molecules such as VCAM and ICAM. In human umbilical vein endothelial cells (HUVECs), compound inhibited tumor necrosis factor (TNF- α)-induced VCAM expression with an IC₅₀ of 2.5 μ M. In a mouse model of asthma, MOL-294 reduced eosinophilia and airways hyperresponsiveness. Potentially useful for the treatment of inflammatory disorders, particularly bronchial asthma.

SOURCE – Molecumetics.

REFERENCES

1. Kahn, M. et al. (Molecumetics Ltd.) *Use of β -sheet mimetics as protease and kinase inhibitors and as inhibitors of transcription factors*. WO 9805333.
2. Misra-Press, A. et al. *Synthesis and biological studies of a novel inhibitor of NF- κ B*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 213.
3. *NF- κ B pathway inhibitor program*. Molecumetics Ltd. Web Site 1999, March 26.

TASP-V

273206

Compound formed by the attachment of NPY 21-36 to a template-assembled synthetic peptide (TASP)

ACTION – Neuropeptide Y (NPY) agonist with subnanomolar affinity for the Y_2 subtype ($K_i = 0.38$ nM) and high selectivity over Y_1 receptors ($K_i = 2$ μ M). In pigs,

intranasal or intrabronchial pretreatment with compound (10 µg/kg) significantly reduced nasal obstruction or bronchoconstriction induced by histamine challenge. In healthy volunteers, intranasal pretreatment with compound (1.275 mg/kg), significantly attenuated (by ~50%) the effects of histamine on both nasal airways resistance and nasal minimal cross-section area. Potentially useful for the treatment of allergic rhinitis and asthma.

SOURCE – Université de Lausanne, Lausanne (CH).

REFERENCES

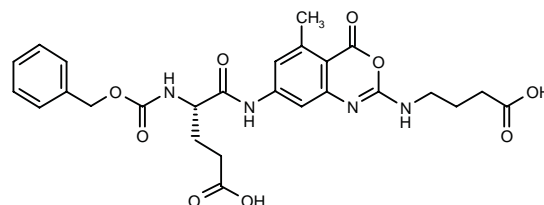
1. Malis, D.-D. et al. *Influence of TASP-V, a novel neuropeptide Y (NPY) Y2 agonist, on nasal and bronchial responses evoked by histamine in anaesthetized pigs and in humans.* Br J Pharmacol 1999, 126(4): 989.

TREATMENT OF RDS AND EMPHYSEMA

TEI-8362*

238488

4-[7-(Benzyloxycarbonyl-L-glutamylamino)-5-methyl-4-oxo-4*H*-3,1-benzoxazin-2-ylamino]butyric acid



C26 H28 N4 O9; Mol wt: 540.5341

ACTION – Human neutrophil elastase (HNE) inhibitor ($K_i = 1.38$ nM) with protective effects against acute lung injury in hamsters: it inhibited lung hemorrhage secondary to lung damage induced by HNE or lipopolysaccharide (LPS) plus fMLP with ED_{50} values of 0.045 intratracheally (i.t.) and 15 mg/kg i.v., and 0.56 mg/kg i.t. and 70 mg/kg i.v., respectively. It is considered a good therapeutic candidate for the treatment of destructive lung diseases mediated by neutrophils.

SOURCE – Teijin.

REFERENCES

1. Fujii, K. et al. (Teijin Ltd.) *High soluble 4H-3,1-benzoxazin-4-one cpds. and their serine protease inhibitory activity*. JP 96134050.
2. Mitsuhashi, H. et al. *Pharmacological activities of TEI-8362, a novel inhibitor of human neutrophil elastase*. Br J Pharmacol 1999, 126(6): 1147.
3. Nonaka, T. et al. *Potency of TEI-8362, a novel neutrophil elastase inhibitor, on acute lung injury models*. Jpn J Pharmacol 1999, 79(Suppl. 1): Abst P-570.

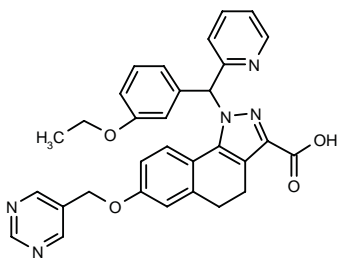
*Identified compound **238488** Drug Data Report 1996, 018(09): 0792.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

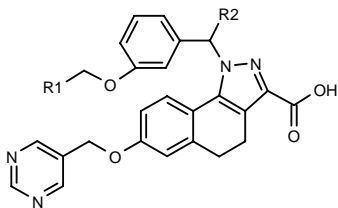
273426

1-[1-(3-Ethoxyphenyl)-1-(2-pyridinyl)methyl]-7-(5-pyrimidinylmethoxy)-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxylic acid



C31 H27 N5 O4; Mol wt: 533.5853

ACTION – Antihypertensive and antianginal agent, an endothelin receptor antagonist with high affinity for both ET_A (IC₅₀ = 2.5 nM) and ET_B receptors (IC₅₀ = 11.3 nM); also reported to inhibit phosphodiesterase type 3 (PDE3; IC₅₀ = 580 nM using enzyme from guinea pig heart homogenates). Within this series of 4,5-dihydro-(1*H*)-benz[*g*]indazole-3-carboxylic acid derivatives, the following are also included:



Compound	R1	R2	Formula
273427	H	H	C ₂₅ H ₂₂ N ₄ O ₄
273428	Me	H	C ₂₆ H ₂₄ N ₄ O ₄
273429	Me	OEt	C ₂₈ H ₂₈ N ₄ O ₅

SOURCE – Teikoku Hormone.

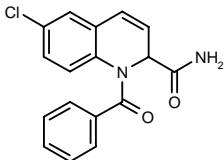
REFERENCES

1. Yamashita, H. et al. (Teikoku Hormone Manufacturing Co., Ltd.) 4,5-Dihydro-[1*H*]-benz[*g*]indazole-3-carboxylic acid derivs. JP 99029569, WO 9902519.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

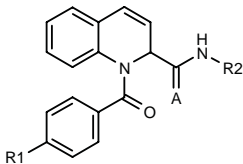
273228

1-Benzoyl-6-chloro-1,2-dihydroquinoline-2-carboxamide



C17 H13 Cl N2 O2; Mol wt: 312.7547

ACTION – Antiatherosclerotic agent that acts by increasing HDL cholesterol levels, as demonstrated *in vivo* in cholesterol-fed rats where it produced a 74% increase in HDL cholesterol levels at a dose of 50 mg/kg/day p.o. x 8 days. Other specifically claimed compounds within this series of 2-substituted-1-acyl-1,2-dihydroquinoline derivatives include the following:



Compound	R1	R2	A	Formula
273229	F	H	O	C ₁₇ H ₁₃ FN ₂ O ₂
273230	CF3	OH	NH	C ₁₈ H ₁₄ F ₃ N ₃ O ₂
273231	F	OH	NH	C ₁₇ H ₁₄ FN ₃ O ₂

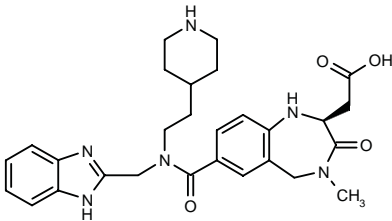
SOURCE – American Home Products.

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1. Babiak, J. et al. (American Home Products Corp.) 2-Substd.-1-acyl-1,2-dihydroquinoline derivs. to increase HDL-cholesterol level. WO 9833775.

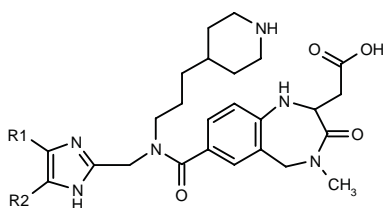
273600

2-[7-[*N*-(1*H*-benzimidazol-2-ylmethyl)-*N*-[2-(4-piperidinyl)ethyl]carbamoyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-2(*S*)-yl]acetic acid



C28 H34 N6 O4; Mol wt: 518.6146

ACTION – Dual vitronectin (α_vβ₃) and fibrinogen (gpIIb/IIIa) receptor antagonist reported to be particularly useful for the treatment of atherosclerosis and restenosis, as well as in preventing tumor growth and metastasis. Other exemplified compounds within this series of integrin receptor antagonists include the following:



Compound	R1,R2	Isomer	Formula
273601	-CH=CHCH=CH-	S	C ₂₉ H ₃₆ N ₆ O ₄
273602	-(CH ₂) ₄ -	S	C ₂₉ H ₄₀ N ₆ O ₄
273603	-CH=CHCH=CH-		C ₂₉ H ₃₆ N ₆ O ₄

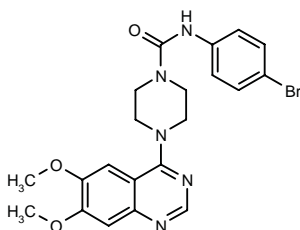
SOURCE – SmithKline Beecham.

REFERENCES

1. Heerding, D. and Samanen, J.M. (SmithKline Beecham Corp.) *Integrin receptor antagonists*. WO 9906049.

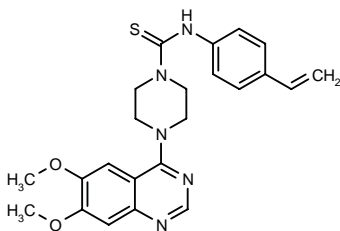
273758

N-(4-Bromophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-piperazine-1-carboxamide



C₂₁ H₂₂ Br N₅ O₃; Mol wt: 472.3408

ACTION – Potent and selective inhibitor of platelet-derived growth factor (PDGF) receptor phosphorylation (IC₅₀ = 0.26 μM). Compound inhibited PDGF-induced smooth muscle cell proliferation with an IC₅₀ value of 0.08 nM. Selected for further evaluation for its potential in the treatment of atherosclerosis, restenosis and cancer. Another related compound is:



273759: C₂₃ H₂₅ N₅ O₂ S

SOURCES – COR Therapeutics; Kyowa Hakko.

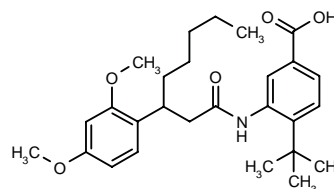
REFERENCES

1. Matsuno, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Nitrogenous heterocyclic cpds*. EP 882717, WO 9814431.

2. Matsuno, K. et al. *Selective inhibitor of PDGF receptor phosphorylation. Synthesis, structure activity relationships and biological effects*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MED1 061.

273856

4-*tert*-Butyl-3-[3-(2,4-dimethoxyphenyl)octanamido]-benzoic acid



C₂₇ H₃₇ N O₅; Mol wt: 455.5913

ACTION – Antiatherosclerotic agent proven to increase the production of apolipoprotein A-I (apoA-I) in HepG2 cells by 41% at 1.25 μg/ml.

SOURCE – Sankyo.

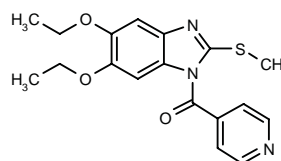
REFERENCES

1. Yoshida, A. et al. (Sankyo Co., Ltd.) *Carboxylic acid derivs*. JP 98316641.

HEART FAILURE THERAPY

272846

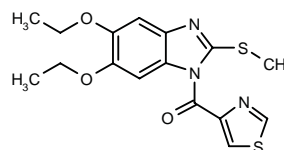
[5,6-Diethoxy-2-(methylsulfanyl)-1*H*-benzimidazol-1-yl](4-pyridinyl)methanone



C₁₈ H₁₉ N₃ O₃ S; Mol wt: 357.4321

M.p. 122-4 °C.

ACTION – Cardiotonic agent with positive inotropic activity (ED₅₀ = 80 μM) in isolated guinea pig papillary muscles, showing comparable potency to milrinone (ED₅₀ = 83 μM), an inhibitor of cAMP phosphodiesterase. Compound appears to act by increasing Ca²⁺ influx into myocardial cells via slow calcium channels. Another compound in this series of benzimidazoles is:



272847: C₁₆ H₁₇ N₃ O₃ S₂

SOURCES – Kaunas Medical University, Kaunas (LT); Vilnius University, Vilnius (LT).

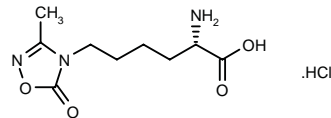
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1. Garaliene, V. et al. *Synthesis and positive inotropic effects of 1-acyl-5,6-diethoxy-2-methylthiobenzimidazoles*. *Arzneim-Forsch Drug Res* 1998, 48(12): 1137.

TREATMENT OF SHOCK

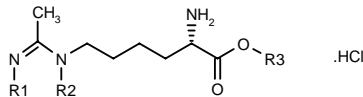
272861

2(S)-Amino-6-[3-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-4-yl]hexanoic acid hydrochloride



C9 H15 N3 O4 . HCl; Mol wt: 265.6954

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the human inducible isoform of the enzyme (iNOS) over the human constitutive isoforms (eNOS and nNOS), with respective IC₅₀ values of 138, 1141 and 159 μM. In rats, it inhibited the increase in plasma nitrite levels elicited by injection of a low dose of endotoxin (LPS) by 39 and 42% at doses of 3 mg/kg/day p.o. and 10 mg/kg/day p.o., respectively. Potentially useful for the treatment of systemic hypotension associated with toxic and septic shock, as well as other conditions characterized by abnormal production of nitric oxide (NO). Within this series of specifically claimed 1,3-diaza-heterocycles, the following are also included:



Compound	R1,R2	R3	Formula
272862	-OCO-	Et	C ₁₁ H ₁₉ N ₃ O ₄ .HCl
272863	-COO-	H	C ₉ H ₁₅ N ₃ O ₄ .HCl

SOURCE – Searle.

REFERENCES

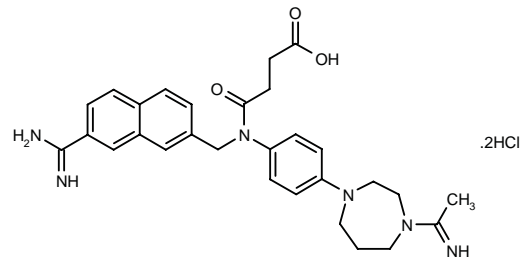
1. Hansen, D.W. Jr. et al. (G.D. Searle & Co.) *1,3-Diaza-heterocycles and their use as nitric oxide synthase inhibitors*. WO 9905131.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

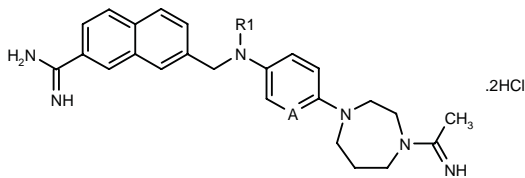
273127

N-[4-(4-Acetimidoyl-1,4-diazepan-1-yl)phenyl]-N-(7-amidino-2-naphthylmethyl)succinamic acid dihydrochloride



C29 H34 N6 O3 . 2HCl; Mol wt: 587.5484

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of factor Xa proven to double the factor Xa coagulation time (CT2) in human plasma at a concentration of 0.069 μM. Other compounds from this series of hexahydro-1,4-diazepine derivatives include the following:



Compound	R1	A	Formula
273134	Ac	CH	C ₂₇ H ₃₂ N ₆ O ₄ .2HCl
273135	SO2CH2CO2H	N	C ₂₆ H ₃₁ N ₇ O ₄ S.2HCl
273137	SO2CH2CO2H	CH	C ₂₇ H ₃₂ N ₆ O ₄ S.2HCl
273138	CSNHCH2CO2H	CH	C ₂₈ H ₃₃ N ₇ O ₂ S.2HCl

SOURCE – Yamanouchi.

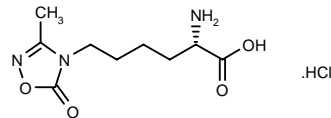
REFERENCES

1. Koshio, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel hexahydro-1,4-diazepine derivs. or salts thereof*. WO 9905124.

TREATMENT OF SHOCK

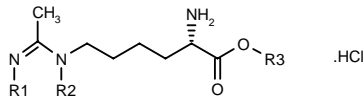
272861

2(S)-Amino-6-[3-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-4-yl]hexanoic acid hydrochloride



C9 H15 N3 O4 . HCl; Mol wt: 265.6954

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the human inducible isoform of the enzyme (iNOS) over the human constitutive isoforms (eNOS and nNOS), with respective IC₅₀ values of 138, 1141 and 159 μM. In rats, it inhibited the increase in plasma nitrite levels elicited by injection of a low dose of endotoxin (LPS) by 39 and 42% at doses of 3 mg/kg/day p.o. and 10 mg/kg/day p.o., respectively. Potentially useful for the treatment of systemic hypotension associated with toxic and septic shock, as well as other conditions characterized by abnormal production of nitric oxide (NO). Within this series of specifically claimed 1,3-diaza-heterocycles, the following are also included:



Compound	R1,R2	R3	Formula
272862	-OCO-	Et	C ₁₁ H ₁₉ N ₃ O ₄ .HCl
272863	-COO-	H	C ₉ H ₁₅ N ₃ O ₄ .HCl

SOURCE – Searle.

REFERENCES

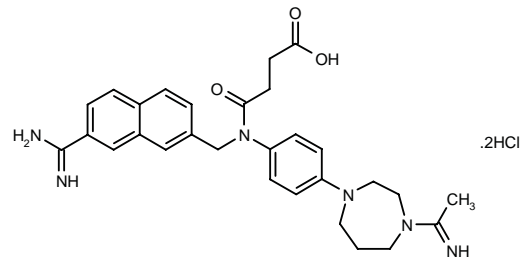
1. Hansen, D.W. Jr. et al. (G.D. Searle & Co.) *1,3-Diaza-heterocycles and their use as nitric oxide synthase inhibitors*. WO 9905131.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

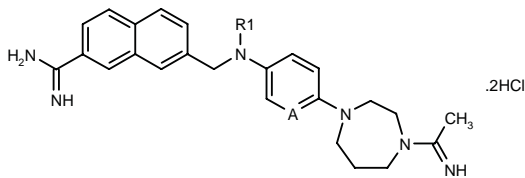
273127

N-[4-(4-Acetimidoyl-1,4-diazepan-1-yl)phenyl]-N-(7-amidino-2-naphthylmethyl)succinamic acid dihydrochloride



C29 H34 N6 O3 . 2HCl; Mol wt: 587.5484

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of factor Xa proven to double the factor Xa coagulation time (CT2) in human plasma at a concentration of 0.069 μM. Other compounds from this series of hexahydro-1,4-diazepine derivatives include the following:



Compound	R1	A	Formula
273134	Ac	CH	C ₂₇ H ₃₂ N ₆ O ₄ .2HCl
273135	SO2CH2CO2H	N	C ₂₆ H ₃₁ N ₇ O ₄ S.2HCl
273137	SO2CH2CO2H	CH	C ₂₇ H ₃₂ N ₆ O ₄ S.2HCl
273138	CSNHCH2CO2H	CH	C ₂₈ H ₃₃ N ₇ O ₄ S.2HCl

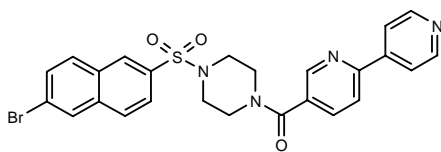
SOURCE – Yamanouchi.

REFERENCES

1. Koshio, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel hexahydro-1,4-diazepine derivs. or salts thereof*. WO 9905124.

273166

1-[4-(6-Bromo-2-naphthylsulfonyl)-1-piperazinyl]-1-[6-(4-pyridyl)pyridin-3-yl]methanone



C25 H21 Br N4 O3 S; Mol wt: 537.4359

ACTION – Antithrombotic agent and anticoagulant that acts by inhibiting factor Xa, representative of a series of heterocyclic compounds.

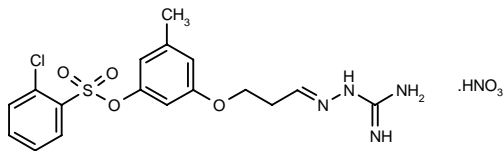
SOURCE – Zeneca (AstraZeneca).

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273757

2-Chlorobenzenesulfonic acid 3-[3-(amidinohydrazono)-propoxy]-5-methylphenyl ester nitrate



C17 H19 Cl N4 O4 S . H N O3; Mol wt: 473.8920

ACTION – Potent, orally active thrombin inhibitor ($K_i = 1.3$ nM) with high selectivity versus several other serine proteases such as factor Xa, urokinase, elastase, chymotrypsin, trypsin and plasmin.

SOURCE – 3-Dimensional.

REFERENCES

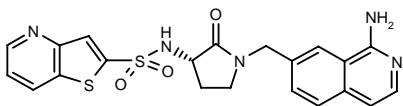
1. Soll, R.M. et al. (3-Dimensional Pharmaceuticals, Inc.) *Amidinohydrazones as protease inhibitors*. EP 906091, US 5891909, WO 9736580.

2. Soll, R.M. et al. (3-Dimensional Pharmaceuticals, Inc.) *Aminoguanidines and alkoxyguanidines as protease inhibitors*. WO 9823565.

3. Lu, T. et al. *Amidinohydrazones as guanidine bioisosteres: Application to a new class of potent, selective and orally bioavailable, non-amide-based small molecular thrombin inhibitors*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 078.

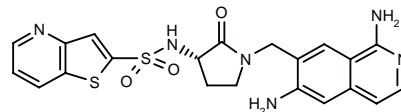
273897

N-[1-(1-Aminoisoquinolin-7-ylmethyl)-2-oxopyrrolidin-3(S)-yl]thieno[3,2-b]pyridine-2-sulfonamide



C21 H19 N5 O3 S2; Mol wt: 453.5451

ACTION – Potent inhibitor of factor Xa ($K_i = 22$ nM) with excellent selectivity (> 2 orders of magnitude) over other serine proteases such as thrombin, trypsin, plasmin, tPA and APC. When given to dogs at a dose of 10 mg/kg p.o., it inhibited *ex vivo* factor Xa activity by 72 and 60% after 2 and 4 h, respectively, with an absolute oral bioavailability of 53%. Potentially useful for the treatment of thrombosis-related diseases such as myocardial infarction, deep vein thrombosis and unstable angina. Another compound from this series of nonbenzamidine inhibitors is:



273898: C21 H20 N6 O3 S2

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Choi-Sledeski, Y. et al. (Rhône-Poulenc Rorer Pharm., Inc.) *Sulfonic or sulfoanilamino N-(heteroaralkyl)-azaheterocyclamide cpds*. WO 9825611.

2. Choi-Sledeski, Y.M. et al. *Design, structure activity relationships and initial biological activity of novel non-benzamidine inhibitors of Factor Xa*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 080.

VASOFLUX™**256550**

Low-molecular weight heparin derivative prepared by depolymerization of heparin, restricting molecular size between 3000 and 8000 Da, and reducing antithrombin affinity by periodate oxidation

ACTION – Antithrombotic agent, a low-molecular-weight heparin derivative chemically modified to reduce its affinity for thrombin that acts by catalyzing the inactivation of fibrin-bound thrombin and factor Xa. The compound blocks clotting within vessels (thrombosis) without affecting the necessary clot formation at sites of injury (hemostasis), and it has a significantly improved antithrombotic and safety profile compared to currently available agents. In phase I clinical trials in healthy volunteers, compound demonstrated a good safety profile and it is now undergoing phase II clinical trials as a potential agent for the treatment of acute cardiovascular disorders such as acute myocardial infarction and ischemic stroke.

SOURCES – Hamilton Civic Hospitals Research Centre, Hamilton, ON (CA); Vascular Therapeutics.

REFERENCES

1. Hirsh, J. et al. (Hamilton Civic Hospitals Research Centre) *Processes for the preparation of low-affinity, low molecular weight heparins useful as antithrombotics*. US 5767269.

2. Spickler, W. et al. *Clinical evaluation of the pharmacology, and safety of Vasoflux™, a novel antithrombotic*. Circulation 1997, 96(8, Suppl.): Abst 216.

3. Spickler, W. et al. *The clinical pharmacology of Vasoflux™ compared to heparin, results of a phase I clinical trial*. J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 1998.

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5. Weitz, J.I. et al. *Vasoflux™, a novel oligosaccharide with unique antithrombotic properties*. Thromb Haemost 1997, Suppl.: Abst PS-2831.

6. Weitz, J.I. et al. *Vasoflux, a new anticoagulant with a novel mechanism of action*. Circulation 1999, 99(5): 682.

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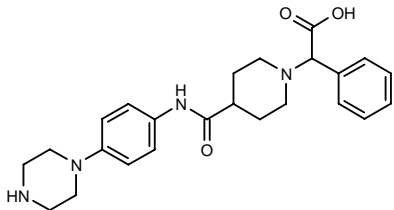
8. *Phase II trial of Vasoflux begins in acute MI*. DailyDrugNews.com (Daily Essentials) 1997, Dec 17.

9. *Vascular Therapeutics reports positive safety and efficacy profile for Vasoflux*. DailyDrugNews.com (Daily Essentials) 1997, April 28.

ANTIPLATELET THERAPY

272851

2-Phenyl-2-[4-[N-[4-(1-piperazinyl)phenyl]carbamoyl]-1-piperidinyl]acetic acid



C24 H30 N4 O3; Mol wt: 422.5260

ACTION – Platelet aggregation inhibitor and anti-thrombotic agent that acts by virtue of its fibrinogen (gpIIb/IIIa) receptor-antagonist activity ($K_i \sim 3.5$ nM against [3 H]-SK&F-1907260 binding).

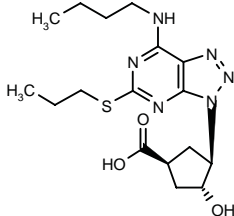
SOURCE – SmithKline Beecham.

REFERENCES

1. Heerding, D. and Samanen, J.M. (SmithKline Beecham Corp.) *Fibrinogen receptor antagonists*. WO 9904796.

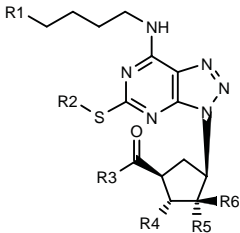
273284

(1*S*,3*R*,4*R*)-3-[7-(Butylamino)-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-4-hydroxycyclopentanecarboxylic acid

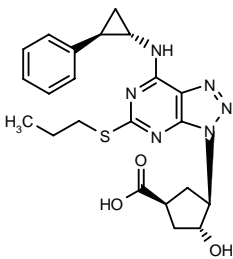


C17 H26 N6 O3 S; Mol wt: 394.4974

ACTION – Platelet aggregation inhibitor and antithrombotic agent that acts as an antagonist at the P2T purinoceptor. Other specifically claimed compounds from this series of substituted triazolo[4,5-*d*]pyrimidines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
273286	H	4-CF3-Ph	OH	H	OH	H	C ₂₁ H ₂₃ F ₃ N ₆ O ₃ S
273287	H	4-CF3-Ph	-L-Ser-OH	H	H	OH	C ₂₄ H ₂₈ F ₃ N ₇ O ₅ S
273288	H	4-CF3-Ph	-Gly-OH	H	H	OH	C ₂₃ H ₂₆ F ₃ N ₇ O ₄ S
273290	H	Pr	-Gly-OH	H	H	OH	C ₁₉ H ₂₉ N ₇ O ₄ S
273291	Et	Pr	OH	H	OH	H	C ₁₉ H ₃₀ N ₆ O ₃ S
273292	H	Pr	OH	OH	H	H	C ₁₇ H ₂₆ N ₆ O ₃ S



273289: C22 H26 N6 O3 S

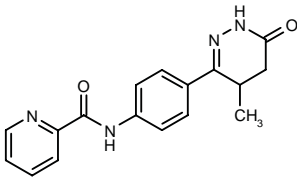
SOURCE – Astra (AstraZeneca).

REFERENCES

1. Brown, R. and Paireudeau, G. (Astra AB;Astra Pharmaceuticals Ltd.) *Novel cpds*. WO 9905144.

273554

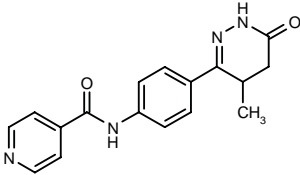
N-[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-phenyl]pyridine-2-carboxamide



C17 H16 N4 O2; Mol wt: 308.3394

M.p. 208-10 °C.

ACTION – Platelet aggregation inhibitor with about 10 times the activity of CI-930 against ADP-induced platelet aggregation. Another 6-(4'-substituted acylaminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone compound is:



273555: C17 H16 N4 O2

SOURCE – Second Military Medical University, Shanghai (CN).

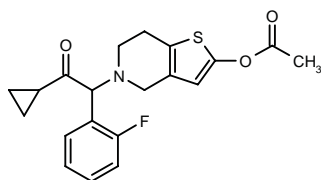
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1. Liu, C.M. et al. *Synthesis and platelet aggregation inhibitory activity of 6-(4'-substituted acylaminophenyl)-4,5-dihydro-3-(2H)-pyridazinones*. Acta Pharm Sin 1999, 34(1): 23.

CS-747

273686

Acetic acid 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl ester



C20 H20 F N O3 S; Mol wt: 373.4460

ACTION – Antiplatelet agent, a potent P2T purinoceptor antagonist. Phase I clinical trials in healthy volunteers demonstrated that a single oral dose of compound (30 or 75 mg) produced rapid (1 h) and long-lasting inhibition (> 48 h) of *ex vivo* ADP- but not collagen-induced platelet aggregation. In a multiple-dose study, 10 mg p.o. inhibited platelet aggregation for at least 2 days after treatment. Compound was devoid of serious side effects. Potentially useful for the treatment or prevention of cardiovascular events such as unstable angina, myocardial infarction or stroke.

SOURCES – Sankyo; Ube.

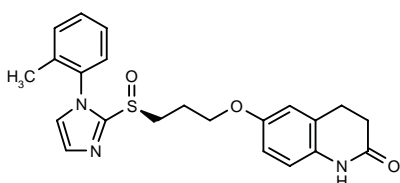
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2. Ataka, K. et al. (Ube Industries, Ltd.) *2-Silyloxytetrahydrothienopyridine, salt thereof and process for preparing the same*. US 5874581, WO 9611203.
3. Hirota, T. et al. *Efficacy of CS-747, a new potent antiplatelet agent*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PII-5.
4. *Focus on Sankyo's R&D activities at home and abroad*. DailyDrugNews.com (Daily Essentials) 1998, Oct 9.
5. *Sankyo overseas clinical pipeline*. DailyDrugNews.com (Daily Essentials) 1998, July 7.

OPC-29030*

217787

(S)-(+)-6-[3-[1-(2-Methylphenyl)imidazol-2-ylsulfanyl]propoxy]-1,2,3,4-tetrahydroquinolin-2-one



C22 H23 N3 O3 S; Mol wt: 409.5110

ACTION – Platelet aggregation inhibitor that acts by inhibiting platelet 12-hydroxyeicosatetraenoic acid (12-HETE) release (IC_{50} = 315 ng/ml for *ex vivo* platelet 12-HETE inhibition in dogs). When infused i.v. for 40 min at a dose of 10 µg/kg/min, it significantly inhibited cyclic flow reductions in stenosed and endothelium-injured canine coronary arteries, as well as *ex vivo* platelet aggregation and 12-HETE formation induced by ADP or U-46619. Compound also inhibited human platelet gplIb/IIIa receptor activation induced by ADP or U-46619, but it did not inhibit cyclooxygenase and did not affect thrombin-stimulated platelet TxA_2 production or intraplatelet cAMP levels. Currently undergoing clinical trials.

SOURCE – Otsuka.

REFERENCES

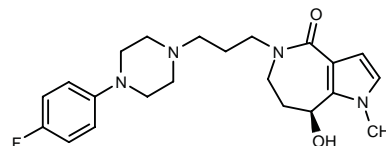
1. Nishi, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Carbostyryl derivs*. EP 651747, JP 95033765, US 5541198, WO 9426732.
2. Katoh, A. et al. *Involvement of 12-HETE in mediating CFVs in severely stenosed and endothelium-injured canine coronary arteries*. Circulation 1997, 96(Suppl. 1): Abst 4047.
3. Katoh, A. et al. *Platelet-derived 12-hydroxyeicosatetraenoic acid plays an important role in mediating canine coronary thrombosis by regulating platelet glycoprotein IIb/IIIa activation*. Circulation 1998, 98(25): 2891.
4. Matsugi, M. et al. *Practical asymmetric oxidation of 3-[1-(2-methylphenyl)imidazol-2-ylthio]propan-1-ol based on a titanium-mandelic acid complex*. Tetrahedron Lett 1998, 39(31): 5591.
5. Morita, S. et al. *Synthesis of a key intermediate, (S)-2-[(3-hydroxypropyl)sulfanyl]-1-(o-tolyl)imidazole, for the antiplatelet aggregation inhibitor, OPC-29030 via lipase-catalyzed enantioselective transesterification*. Tetrahedron Asymmetry 1997, 8(22): 3707.
6. Uno, T. et al. *Synthesis of 2(1H)-quinolinone derivatives and their inhibitory activity on the release of 12(S)-hydroxyeicosatetraenoic acid (12-HETE) from platelets*. Chem Pharm Bull 1995, 43(10): 1724.
7. Uno, T. et al. *Synthesis of 2(1H)-quinolinone derivatives and their inhibitory activity on the release of 12-HETE from platelets*. 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 2-P-20.

*Identified compound **217787** Drug Data Report 1995, 017(04): 0342.

SUN-C5174

273797

5-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-8(S)-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-c]-azepin-4-one



C22 H29 F N4 O2; Mol wt: 400.4951

ACTION – Potent, selective and orally active 5-HT₂ receptor antagonist with an IC_{50} value of 4.3 nM against [³H]-ketanserin binding in rat brain membranes and a pA_2 of 9.0 in isolated guinea pig arteries stimulated by 5-HT. Compound inhibited *in vitro* rabbit platelet aggregation induced by 5-HT, ADP and collagen with IC_{50} values ranging from 6.5 to 16 nM, as well as *ex vivo* dog platelet aggregation (ED_{50} = 0.02 mg/kg p.o.). It also inhibited vasoconstriction in rabbit vessels induced by thrombin-aggregated platelet-rich plasma. Results from animal studies indicated potential in the treatment of peripheral circulatory disorders.

SOURCE – Suntory.

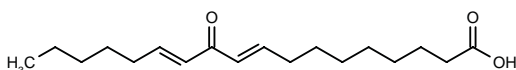
REFERENCES

1. Mizuno, A. et al. (Suntory Ltd.) *Pyrroloazepine derivs.* EP 807632, WO 9720845.
2. Inomata, N. et al. *Pharmacological characterization of a novel, selective and potent 5-HT₁ receptor antagonist, SUN C5174.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-255.
3. Ogata, A. et al. *Effect of SUN C5174, a novel 5-HT₂ receptor antagonist, on various experimental models of peripheral circulatory disturbance.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-288.
4. *Suntory initiates clinical testing of three new compounds.* DailyDrugNews.com (Daily Essentials) 1998, June 17.

THROMBOLYTICS

273091

11-Oxo-9(*E*),12(*E*)-octadecadienoic acid



C18 H30 O3; Mol wt: 294.4320

Light brown oil.

ACTION – An agent that enhances the fibrinolytic activity of endothelial cells, a fatty acid isolated from *Trichoderma* sp. F5594. It increased by 1.5-4-fold the fibrinolytic activity of cultured bovine aortic endothelial cells at concentrations of 50-650 μ M. Potentially useful for the prevention of vascular diseases such as thromboembolic disorders and atherosclerosis.

SOURCE – Tokyo Noko University, Tokyo (JP).

REFERENCES

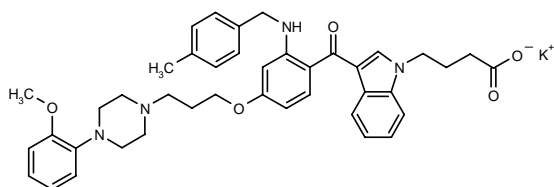
1. Shinohara, C. et al. *11-Keto-9(E),12(E)-octadecadienoic acid, a novel fatty acid that enhances fibrinolytic activity of endothelial cells.* J Antibiot 1999, 52(2): 171.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

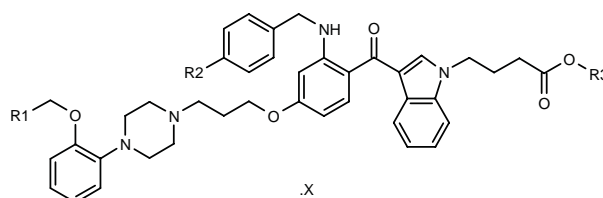
273149

4-[3-[4-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propoxy]-2-(4-methylbenzylamino)benzoyl]-1*H*-indol-1-yl]butyric acid potassium salt



C41 H45 K N4 O5; Mol wt: 712.9275

ACTION – Agent for the treatment of benign prostatic hypertrophy, baldness or acne, an inhibitor of 5 α -reductase (IC_{50} = 0.86 nM against enzyme from rat prostate) with additional α_1 -adrenoceptor-blocking activity, as demonstrated in rabbit urethra and prostate preparations (pA_2 = 6.76 and 7.27, respectively). Within this series of 3-benzoylindole derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
273150	H	Et	H	HCl	C ₄₂ H ₄₈ N ₄ O ₅ ·HCl
273151	H	H	K		C ₄₀ H ₄₃ KN ₄ O ₅
273152	Me	Et	H		C ₄₃ H ₅₀ N ₄ O ₅
273153	Me	Me	H		C ₄₂ H ₄₈ N ₄ O ₅

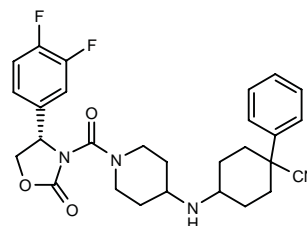
SOURCE – Zeria.

REFERENCES

1. Sato, H. et al. (Zeria Pharmaceutical Co., Ltd.) *3-Benzoylindole derivs. and drugs containing the same.* JP 99035558, WO 9903831.

273932

4-[1-[4(*S*)-(3,4-Difluorophenyl)-2-oxooxazolidin-3-yl]-carbonyl]piperidin-4-ylamino]-1-phenylcyclohexane-carbonitrile



C28 H30 F2 N4 O3; Mol wt: 508.5660

ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a human α_{1a} -adrenoceptor antagonist reported to possess at least 10-fold lower affinity for human α_{1b} - and α_{1d} -adrenoceptors; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. A representative compound from a series of 1,4-disubstituted piperidine derivatives.

SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. and Bock, M.G. (Merck & Co., Inc.) *α_{1a} -Adrenergic receptor antagonists.* WO 9857639.

SOURCE – Suntory.

REFERENCES

1. Mizuno, A. et al. (Suntory Ltd.) *Pyrroloazepine derivs.* EP 807632, WO 9720845.

2. Inomata, N. et al. *Pharmacological characterization of a novel, selective and potent 5-HT₁ receptor antagonist, SUN C5174.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-255.

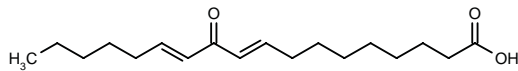
3. Ogata, A. et al. *Effect of SUN C5174, a novel 5-HT₂ receptor antagonist, on various experimental models of peripheral circulatory disturbance.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-288.

4. *Suntory initiates clinical testing of three new compounds.* DailyDrugNews.com (Daily Essentials) 1998, June 17.

THROMBOLYTICS

273091

11-Oxo-9(*E*),12(*E*)-octadecadienoic acid



C18 H30 O3; Mol wt: 294.4320

Light brown oil.

ACTION – An agent that enhances the fibrinolytic activity of endothelial cells, a fatty acid isolated from *Trichoderma* sp. F5594. It increased by 1.5-4-fold the fibrinolytic activity of cultured bovine aortic endothelial cells at concentrations of 50-650 μ M. Potentially useful for the prevention of vascular diseases such as thromboembolic disorders and atherosclerosis.

SOURCE – Tokyo Noko University, Tokyo (JP).

REFERENCES

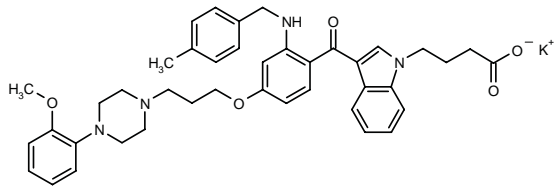
1. Shinohara, C. et al. *11-Keto-9(E),12(E)-octadecadienoic acid, a novel fatty acid that enhances fibrinolytic activity of endothelial cells.* J Antibiot 1999, 52(2): 171.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

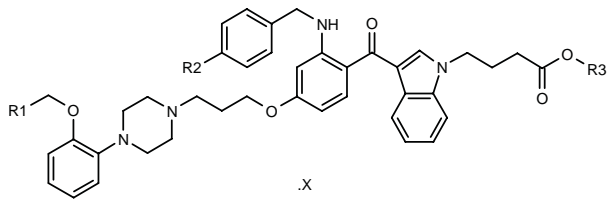
273149

4-[3-[4-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propoxy]-2-(4-methylbenzylamino)benzoyl]-1*H*-indol-1-yl]butyric acid potassium salt



C41 H45 K N4 O5; Mol wt: 712.9275

ACTION – Agent for the treatment of benign prostatic hypertrophy, baldness or acne, an inhibitor of 5 α -reductase (IC₅₀ = 0.86 nM against enzyme from rat prostate) with additional α_1 -adrenoceptor-blocking activity, as demonstrated in rabbit urethra and prostate preparations (pA₂ = 6.76 and 7.27, respectively). Within this series of 3-benzoylindole derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
273150	H	Et	H	HCl	C ₄₂ H ₄₈ N ₄ O ₅ ·HCl
273151	H	H	K		C ₄₀ H ₄₃ KN ₄ O ₅
273152	Me	Et	H		C ₄₃ H ₅₀ N ₄ O ₅
273153	Me	Me	H		C ₄₂ H ₄₈ N ₄ O ₅

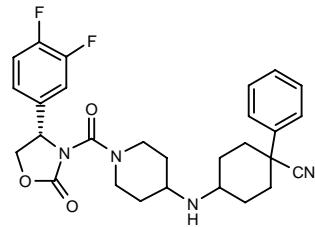
SOURCE – Zeria.

REFERENCES

1. Sato, H. et al. (Zeria Pharmaceutical Co., Ltd.) *3-Benzoylindole derivs. and drugs containing the same.* JP 99035558, WO 9903831.

273932

4-[1-[4(*S*)-(3,4-Difluorophenyl)-2-oxooxazolidin-3-yl]-carbonyl]piperidin-4-ylamino]-1-phenylcyclohexane-carbonitrile



C28 H30 F2 N4 O3; Mol wt: 508.5660

ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a human α_{1a} -adrenoceptor antagonist reported to possess at least 10-fold lower affinity for human α_{1b} - and α_{1d} -adrenoceptors; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. A representative compound from a series of 1,4-disubstituted piperidine derivatives.

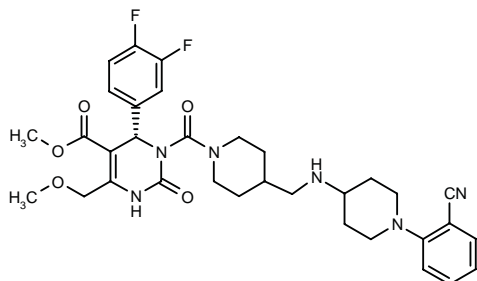
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. and Bock, M.G. (Merck & Co., Inc.) *α_{1a} -Adrenergic receptor antagonists.* WO 9857639.

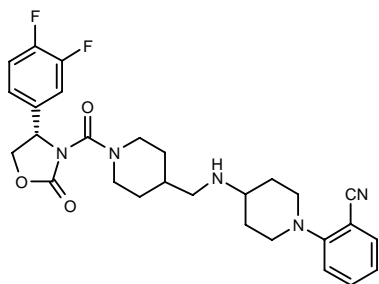
273936

3-[4-[1-(2-Cyanophenyl)piperidin-4-ylaminomethyl]piperidin-1-ylcarbonyl]-4(S)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester



C33 H38 F2 N6 O5; Mol wt: 636.6962

ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a selective human α_{1a} -adrenoceptor antagonist; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. Another specifically claimed compound from this series of piperidine derivatives is:



273938: C28 H31 F2 N5 O3

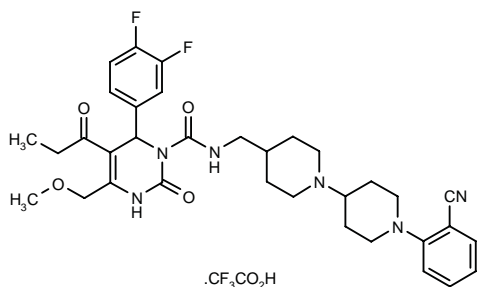
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. and Bock, M.G. (Merck & Co., Inc.) α_{1a} -Adrenergic receptor antagonists. WO 9857642.

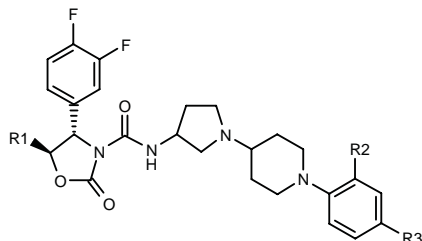
274278

3-[N-[1-[1-(2-Cyanophenyl)piperidin-4-yl]piperidin-4-ylmethyl]carbamoyl]-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester trifluoroacetate

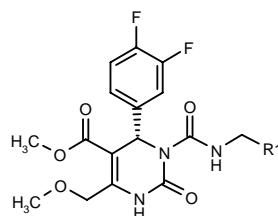


C34 H40 F2 N6 O4 . C2 H F3 O2; Mol wt: 748.7459

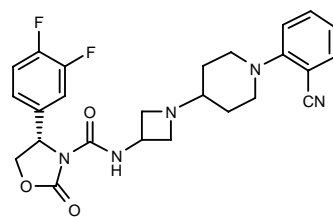
ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a human α_{1a} -adrenoceptor antagonist reported to possess at least 10-fold lower affinity for human α_{1b} - and α_{1d} -adrenoceptors and many other G-protein-coupled receptors; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. A representative compound from a series of 1-(4-piperidinyl)piperidine derivatives, wherein the following are also included:



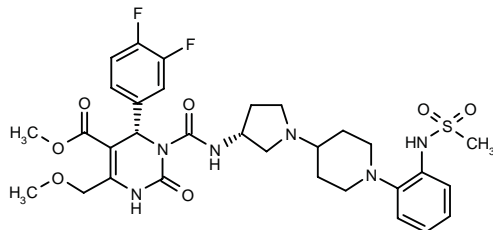
Compound	R1	R2	R3	Isomer	Formula
274280	CO2Me	3-Me-1,2,4-oxadiazol-5-yl	F		C ₃₀ H ₃₁ F ₃ N ₆ O ₆
274281	CONH2	OMe	F		C ₂₇ H ₃₀ F ₃ N ₆ O ₅
274284	H	NHSO2Me	H	R	C ₂₈ H ₃₁ F ₂ N ₆ O ₅ S



Compound	R1	Formula
274283	1-[1-(2-CN-Ph)-4-Pip]-3-OH-3-azetidiny	C ₃₁ H ₃₄ F ₂ N ₆ O ₆
274286	1-[1-(2-CN-Ph)-4-Pip]-3-pyrrolidiny	C ₃₂ H ₃₆ F ₂ N ₆ O ₅
274287	1-[1-(2-CN-Ph)-4-Pip]-3-Pip	C ₃₃ H ₃₈ F ₂ N ₆ O ₅
274289	1-[1-(2-CN-Ph)-4-Pip]-4-Pip	C ₃₃ H ₃₈ F ₂ N ₆ O ₅



274282: C25 H25 F2 N5 O3



274285: C31 H38 F2 N6 O7 S

SOURCE – Merck & Co.

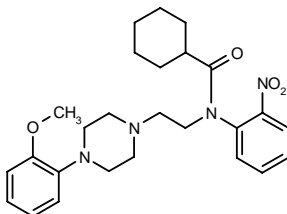
REFERENCES

1. Patane, M.A. and Bock, M.G. (Merck & Co., Inc.) α_{1a} Adrenergic receptor antagonists. WO 9857640.

TREATMENT OF URINARY INCONTINENCE

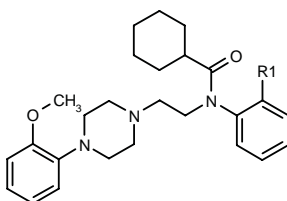
273181

N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-nitrophenyl)cyclohexanecarboxamide



C₂₆H₃₄N₄O₄; Mol wt: 466.5786

ACTION – Agent for the treatment of neuromuscular dysfunction of the lower urinary tract including urinary incontinence, a potent and selective 5-HT_{1A} receptor antagonist ($K_i = 0.05$ nM; K_i 5-HT_{2A} receptors and α_2 -adrenoceptors > 10,000 nM) capable of reducing rhythmic bladder voiding contractions in anesthetized rats (ED₅₀ = 9 µg/kg i.v.; ED₅₀ oxybutynin > 10,000 µg/kg i.v.) without affecting bladder contractility. It also produced a significant increase in bladder volume capacity after i.v. administration of 0.3 mg/kg in conscious rats. Significant pre- and postsynaptic 5-HT_{1A} receptor-antagonist activity was observed in mice and rats, respectively, with ID₅₀ values of 20 and 36 mg/kg i.v. for antagonism of 8-OH-DPAT-induced hypothermia in mice (presynaptic) and of 8-OH-DPAT-induced forepaw treading in rats (postsynaptic). A representative compound within a series of specifically claimed 1-(*N*-phenylaminoalkyl)-piperazine derivatives, wherein the following are also included:



Compound	R1	Formula
273182	I	C ₂₆ H ₃₄ N ₄ O ₂
273183	CO ₂ Me	C ₂₈ H ₃₇ N ₄ O ₄

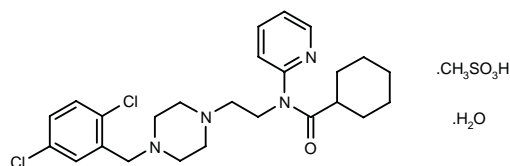
SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) 1-(*N*-Phenylaminoalkyl)-piperazine derivs. substd. at position 2 of the phenyl ring. WO 9906384.

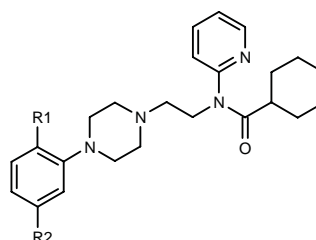
273502

N-[2-[4-(2,5-Dichlorobenzyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide methanesulfonate hydrate



C₂₅H₃₂Cl₂N₄O . C₄H₄O₃S . H₂O; Mol wt: 589.5812

ACTION – Agent for the treatment of neuromuscular dysfunction of the lower urinary tract, particularly urinary incontinence, dysuria and enuresis, with 5-HT_{1A} receptor-antagonist activity ($K_i = 0.12$ nM). *In vivo*, compound was shown to dose-dependently (30-300 mg/kg) suppress volume-induced rhythmic bladder voiding contractions in rats following i.v. administration, being more potent than flavoxate, without affecting bladder contractility. Other compounds within this series of specifically claimed 1,4-disubstituted piperazines include the following:



Compound	R1	R2	Formula
273503	OCF ₃	H	C ₂₅ H ₃₁ F ₃ N ₄ O ₂
273504	OCH ₂ CF ₃	H	C ₂₆ H ₃₃ F ₃ N ₄ O ₂
273505	OCH ₂ CF ₃	Cl	C ₂₆ H ₃₂ ClF ₃ N ₄ O ₂
273506	CN	H	C ₂₅ H ₃₁ N ₅ O
273507	Cl	Cl	C ₂₄ H ₃₀ Cl ₂ N ₄ O

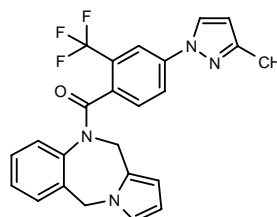
SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) 1,4-Disubstd. piperazines. WO 9906382.

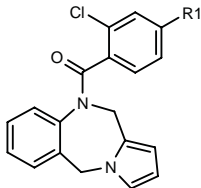
273508

1-[4-(3-Methyl-1*H*-pyrazol-1-yl)-2-(trifluoromethyl)phenyl]-1-[10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-yl]methanone



C₂₄H₁₉F₃N₄O; Mol wt: 436.4351

ACTION – Specific vasopressin V₂ receptor agonist whose activity was demonstrated in normal conscious water-loaded rats, where it produced an 80% decrease in urine volume and a 306% increase in urine osmolality at 1 mg/kg p.o. Claimed for the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence and bleeding or coagulation disorders. Other compounds within this series of tricyclic derivatives include the following:



Compound	R1	Formula
273509	1,2,4-triazol-1-yl	C ₂₁ H ₁₆ ClN ₅ O
273510	1-pyrazolyl	C ₂₂ H ₁₇ ClN ₄ O
273511	1-Me-3-pyrazolyl	C ₂₃ H ₁₉ ClN ₄ O
273512	3-Me-1,2,4-triazol-5-yl	C ₂₂ H ₁₈ ClN ₅ O
273513	1,2,4-triazol-3-yl	C ₂₁ H ₁₆ ClN ₅ O

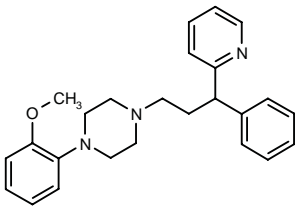
SOURCE – American Home Products.

REFERENCES

1. Dusza, J.P. et al. (American Home Products Corp.) *Tricyclic vasopressin agonists*. WO 9906409.

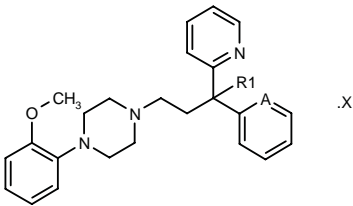
273545

1-(2-Methoxyphenyl)-4-[3-phenyl-3-(2-pyridinyl)-propyl]piperazine



C25 H29 N3 O; Mol wt: 387.5241

ACTION – Agent for the treatment of neuromuscular dysfunction of the lower urinary tract including urinary incontinence, a 5-HT_{1A} receptor antagonist (K_i = 0.62 nM using recombinant human receptor) with high selectivity relative to 5-HT_{2A} receptors and α₁-adrenoceptors (K_i = 1023 and 268 nM, respectively); it was shown to reduce rhythmic bladder voiding contractions in anesthetized rats (ED₅₀ = 25 μg/kg i.v.; ED₅₀ oxybutynin, flavoxate and imipramine = 10,000, 2648 and 4930 μg/kg i.v., respectively). Unlike reference compounds, it did not impair bladder contractility. A representative compound within a series of specifically claimed piperazine derivatives, wherein the following are also included:



Compound	R1	A	X	Formula
273546	CN	CH	2HCl	C ₂₈ H ₂₈ N ₄ O.2HCl
273547	H	N		C ₂₄ H ₂₈ N ₄ O
273548	OH	N		C ₂₄ H ₂₈ N ₄ O ₂

SOURCE – Recordati.

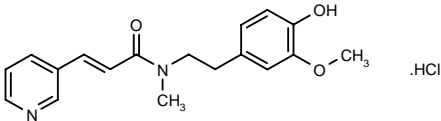
REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Piperazine derivs. active on the lower urinary tract*. WO 9906383.

TREATMENT OF RENAL DISEASES

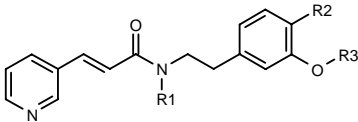
273144

N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-N-methyl-3-(3-pyridinyl)-2(E)-propenamide hydrochloride



C18 H20 N2 O3 . HCl; Mol wt: 348.8279

ACTION – Agent for the treatment of renal diseases such as nephritis proven to reduce proteinuria, serum cholesterol and BUN in a murine model of nephritis induced by rabbit anti-GBM serum following oral administration. Compound was also shown to inhibit transforming growth factor-β₁ (TGF-β₁) production by 78% in glomerulus of mice with rabbit anti-GBM serum-induced nephritis at 1 μM. A representative compound from a series of pyridylacrylamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
273145	H	H	H	C ₁₈ H ₁₈ N ₂ O ₂
273146	Me	OMe	Me	C ₁₉ H ₂₂ N ₂ O ₃
273147	H	H	CH2CO2H	C ₁₈ H ₁₈ N ₂ O ₄

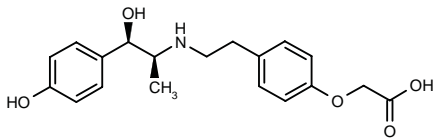
SOURCE – Tsumura.

REFERENCES

1. Hasegawa, Y. et al. (Tsumura & Co.) *Pyridylacrylamide derivs. and nephritis remedies and TGF-β inhibitors containing the same*. WO 9905109.

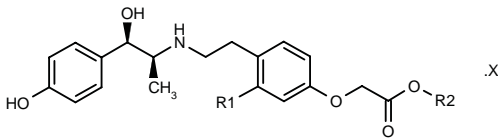
273733

2-[4-[2-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methyl-ethylamino]ethyl]phenoxy]acetic acid



C19 H23 N O5; Mol wt: 345.3927

ACTION – β_2 - And β_3 -adrenoceptor agonist (EC_{50} = 31 and 14 nM, respectively, in pregnant rat uterus and ferret ureter) with reduced activity at β_1 -adrenoceptors (EC_{50} = 1.3 μ M in rat atrium), potentially useful for the treatment of pain and as a lithagogue for the treatment of urinary calculus. No mortality was observed following a single dose of 1000 mg/kg i.v. to rats. Other compounds from this series of aminoethylphenoxyacetic acid derivatives include the following:



Compound	R1	R2	X	Formula
273734	F	CH2Ph	HCl	C ₂₆ H ₂₈ FNO ₅ .HCl
273735	Cl	H		C ₁₉ H ₂₂ ClNO ₅
273736	F	H		C ₁₉ H ₂₂ FNO ₅

SOURCE – Kissei.

REFERENCES

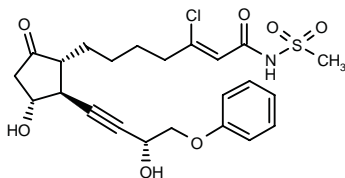
1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *Aminoethylphenoxyacetic acid derivs. and drugs for pain remission and calculi removal promotion in urinary lithiasis.* WO 9905090.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

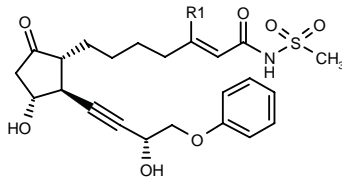
272843

(2*Z*)-3-Chloro-*N*-(methylsulfonyl)-16-phenoxy-2,3,13,14-tetradehydro-17,18,19,20-tetranorprostaglandin E₁ amide



C23 H28 Cl N O7 S; Mol wt: 497.9932

ACTION – Antiulcer agent that inhibits gastric acid secretion apparently by interacting with EP₃ receptors, as demonstrated by its ability to inhibit guinea pig vas deferens contractions elicited by electrical stimulation (IC_{50} = 0.04 nM). Compound has a low liability for inducing diarrhea in mice (ED_{50} > 3.0 mg/kg s.c.). Other exemplified prostaglandin E analogues include the following:



Compound	R1	Isomer	Formula
272844	Me	EZ	C ₂₄ H ₃₁ NO ₇ S
272845	H	E	C ₂₃ H ₂₉ NO ₇ S

SOURCE – Taisho.

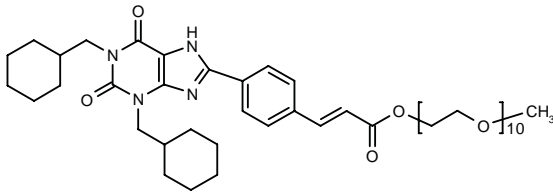
REFERENCES

1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin E analogues.* JP 99012249.

INFLAMMATORY BOWEL DISEASE THERAPY

272741

4-[1,3-Bis(cyclohexylmethyl)xanthin-8-yl]cinnamic acid 3,6,9,12,15,18,21,24,27,30-decaoxahentriacontyl ester

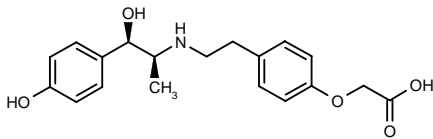


C49 H76 N4 O14; Mol wt: 945.1534

ACTION – Agent for the treatment of inflammatory and immune disorders, an inhibitor of the expression of adhesion molecules. Compound was active *in vivo* in a model of carrageenan pleurisy in rats, with ED_{50} of 0.02 mg/rat for inhibition of inflammatory cells (neutrophils) and 0.2 mg/rat for inhibition of pleural edema (ED_{50} dexamethasone = 0.02 and 0.015 mg/rat, respectively). Compound was also active in an acetic acid-induced colitis assay in rats, as demonstrated by inhibition of edema formation and reduction in mucosal myeloperoxidase (MPO) levels (active dose: 5.0 mg/kg rectally). It also protected against mortality in sensitized mice treated with *Corynebacterium parvum* and *Escherichia coli* 026:B6 lipopolysaccharide, with 50% survival at a dose of 75 mg/kg p.o. vs. 0% in controls.

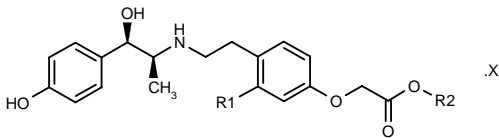
273733

2-[4-[2-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-1(*S*)-methyl-ethylamino]ethyl]phenoxy]acetic acid



C19 H23 N O5; Mol wt: 345.3927

ACTION – β_2 - And β_3 -adrenoceptor agonist (EC_{50} = 31 and 14 nM, respectively, in pregnant rat uterus and ferret ureter) with reduced activity at β_1 -adrenoceptors (EC_{50} = 1.3 μ M in rat atrium), potentially useful for the treatment of pain and as a lithagogue for the treatment of urinary calculus. No mortality was observed following a single dose of 1000 mg/kg i.v. to rats. Other compounds from this series of aminoethylphenoxyacetic acid derivatives include the following:



Compound	R1	R2	X	Formula
273734	F	CH2Ph	HCl	C ₂₆ H ₂₈ FNO ₅ .HCl
273735	Cl	H		C ₁₉ H ₂₂ ClNO ₅
273736	F	H		C ₁₉ H ₂₂ FNO ₅

SOURCE – Kissei.

REFERENCES

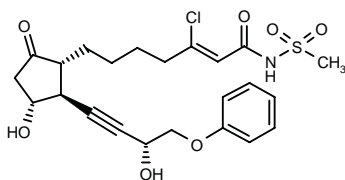
1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *Aminoethylphenoxyacetic acid derivs. and drugs for pain remission and calculi removal promotion in urinary lithiasis.* WO 9905090.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

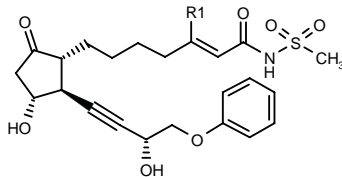
272843

(2*Z*)-3-Chloro-*N*-(methylsulfonyl)-16-phenoxy-2,3,13,14-tetradehydro-17,18,19,20-tetranorprostaglandin E₁ amide



C23 H28 Cl N O7 S; Mol wt: 497.9932

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Compound	R1	Isomer	Formula
272844	Me	EZ	C ₂₄ H ₃₁ NO ₇ S
272845	H	E	C ₂₃ H ₂₉ NO ₇ S

SOURCE – Taisho.

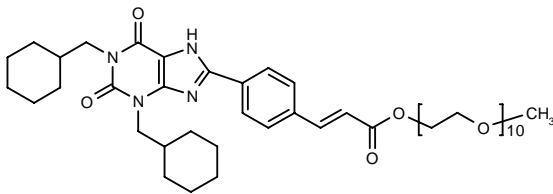
REFERENCES

1. Sato, F. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin E analogues.* JP 99012249.

INFLAMMATORY BOWEL DISEASE THERAPY

272741

4-[1,3-Bis(cyclohexylmethyl)xanthin-8-yl]cinnamic acid 3,6,9,12,15,18,21,24,27,30-decaoxahentriacontyl ester



C49 H76 N4 O14; Mol wt: 945.1534

ACTION – Agent for the treatment of inflammatory and immune disorders, an inhibitor of the expression of adhesion molecules. Compound was active *in vivo* in a model of carrageenan pleurisy in rats, with ED_{50} of 0.02 mg/rat for inhibition of inflammatory cells (neutrophils) and 0.2 mg/rat for inhibition of pleural edema (ED_{50} dexamethasone = 0.02 and 0.015 mg/rat, respectively). Compound was also active in an acetic acid-induced colitis assay in rats, as demonstrated by inhibition of edema formation and reduction in mucosal myeloperoxidase (MPO) levels (active dose: 5.0 mg/kg rectally). It also protected against mortality in sensitized mice treated with *Corynebacterium parvum* and *Escherichia coli* 026:B6 lipopolysaccharide, with 50% survival at a dose of 75 mg/kg p.o. vs. 0% in controls.

SOURCE – Glaxo Wellcome.

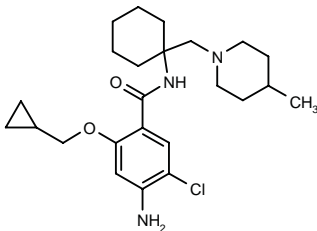
REFERENCES

1. Daluge, S.M. et al. (Glaxo Wellcome plc) *Substd. (1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)phenyl derivs., their preparation and their use in the treatment of inflammatory conditions and immune disorders.* WO 9835966.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

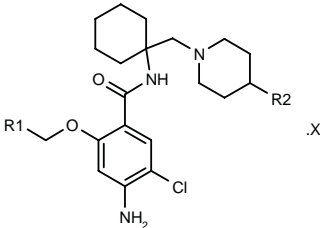
273017

4-Amino-5-chloro-2-(cyclopropylmethoxy)-N-[1-(4-methyl-1-piperidinylmethyl)cyclohexyl]benzamide



C24 H36 Cl N3 O2; Mol wt: 434.0204

ACTION – Gastrointestinal motility stimulant effective in both the upper and lower gastrointestinal tract, also reported to possess analgesic activity. Within this series of cycloalkyl benzamides, the following are also included:



Compound	R1	R2	X	Formula
273018	cyclopropyl	Pr		C ₂₆ H ₄₀ ClN ₃ O ₂
273019	cyclopropyl	H		C ₂₃ H ₃₄ ClN ₃ O ₂
273020	cyclopropyl	Et		C ₂₅ H ₃₈ ClN ₃ O ₂
273021	cyclopropyl	OH		C ₂₃ H ₃₄ ClN ₃ O ₃
273022	H	Me	HCl	C ₂₁ H ₃₂ ClN ₃ O ₂ .HCl
273023	Me	Me		C ₂₂ H ₃₄ ClN ₃ O ₂

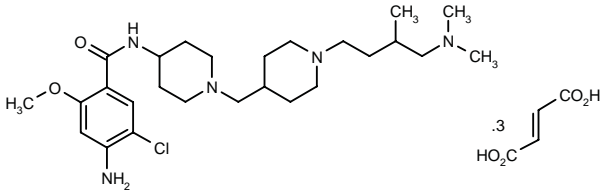
SOURCE – Jacques Logeais.

REFERENCES

1. Jeanpetit, C. et al. (Laboratoires Jacques Logeais) *Benzamide cycloalkyl stimulating high and low gastrointestinal motricity.* WO 9905133.

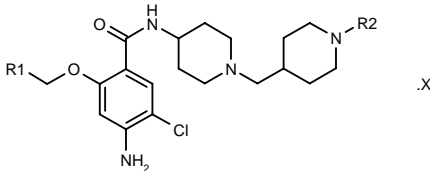
273375

4-Amino-5-chloro-N-[1-[1-[4-(dimethylamino)-3-methyl-butyl]-4-piperidinylmethyl]-4-piperidinyl]-2-methoxybenzamide trifumarate



C26 H44 Cl N5 O2 . 3 C4 H4 O4; Mol wt: 842.3344

ACTION – Gastrointestinal function-enhancing agent, a 5-HT₄ receptor agonist (IC₅₀ = 1.5 nM against [³H]-GR-113808 binding in guinea pig striatum preparations; IC₅₀ cisapride = 23.0 nM). A representative compound from a series of benzamide derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
273376	H	COCH(Ph)NH ₂	dioxalate	C ₂₇ H ₃₆ ClN ₅ O ₃ .2C ₂ H ₂ O ₄
273377	H	(CH ₂) ₃ CH(NH ₂)CH ₂ OH		C ₂₄ H ₄₀ ClN ₅ O ₃
273378	H	(CH ₂) ₃ NH ₂		C ₂₂ H ₃₆ ClN ₅ O ₂
273379	H	(S)-(CH ₂) ₃ CH(NH ₂)CH ₂ OH		C ₂₄ H ₄₀ ClN ₅ O ₃
273380	H	i-PrCH(NH ₂)CH ₂ CO	difumarate	C ₂₅ H ₄₀ ClN ₅ O ₃ .2C ₄ H ₄ O ₄
273381	H	COCH ₂ CH(Ph)NH ₂	difumarate	C ₂₈ H ₃₈ ClN ₅ O ₃ .2C ₄ H ₄ O ₄
273382	H	COCH ₂ C(Me) ₂ NH ₂	difumarate	C ₂₄ H ₃₈ ClN ₅ O ₃ .2C ₄ H ₄ O ₄
273383	H	COCH ₂ CH(OH)CH ₂ NH ₂	difumarate	C ₂₃ H ₃₆ ClN ₅ O ₄ .2C ₄ H ₄ O ₄
273384	H	3-Pip-CO		C ₂₅ H ₃₈ ClN ₅ O ₃
273385	H	CH ₂ CH(NH ₂)CH ₂ CH ₂ NH ₂		C ₂₃ H ₃₉ ClN ₆ O ₂
273386	Me	(CH ₂) ₄ NH ₂		C ₂₄ H ₄₀ ClN ₅ O ₂

SOURCE – Dainippon Pharmaceutical.

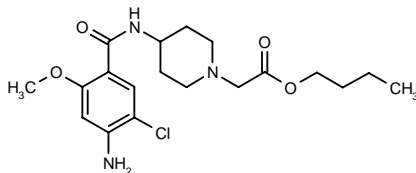
REFERENCES

1. Kato, S. et al. (Dainippon Pharmaceutical Co., Ltd.) *Benzamido derivs. and medicinal compsns. containing the same.* JP 99001472.

AU-224

273798

4-(4-Amino-5-chloro-2-methoxybenzamido)piperidine-1-acetic acid butyl ester



C19 H28 Cl N3 O4; Mol wt: 397.9002

ACTION – Colonic prokinetic agent, an ester-type prodrug of AU-130* that increases colonic activity through the activation of cholinergic neurons and 5-HT₄ receptors. In dogs, compound dose-dependently enhanced colonic motility and induced bowel contractions and defecation in the dose range of 0.03-0.3 i.v. and 1-10 mg/kg p.o. In rats, it accelerated colonic transit and fecal pellet output at 1-10 mg/kg p.o. Compound did not induce watery diarrhea in either species. The effects of AU-244 were completely inhibited in dogs by pretreatment with atropine, the 5-HT₄ receptor antagonist SB-207266 but not the 5-HT₃ receptor antagonist granisetron.

SOURCE – Hokuriku.

REFERENCES

1. Ito, Y. et al. (Hokuriku Seiyaku Co., Ltd.) *Benzamide derivs.* EP 640601, US 5395832, US 5500422, WO 9214705.

2. Saito, T. et al. *Effect of novel colonic prokinetic agents, AU-130 and AU-224, on intestinal motility and defecation in rats and dogs.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-325.

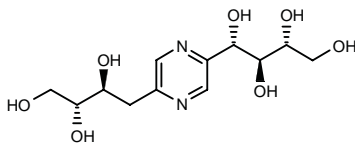
*Drug Data Rep 1998, 020(09): 0780.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

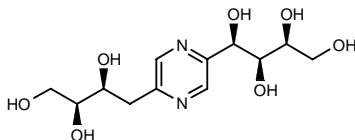
272809

(1*S*,2*S*,3*R*)-1-[5-[(2*S*,3*R*)-2,3,4-Trihydroxybutyl]-2-pyrazinyl]-1,2,3,4-butanetetraol

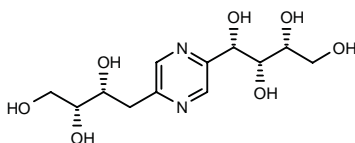


C₁₂ H₂₀ N₂ O₇; Mol wt: 304.2970

ACTION – Hypoglycemic agent, as demonstrated in mice with glycemia induced by an oral glucose load administered doses of 3-50 mg/kg p.o. It has low acute toxicity (LD₅₀ > 2000 mg/kg p.o.) in mice. Within this series of specifically claimed polyhydroxyalkylpyrazine derivatives, the following are also included:



272814: C₁₂ H₂₀ N₂ O₇



272815: C₁₂ H₂₀ N₂ O₇

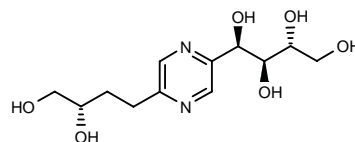
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Bashiardes, G. et al. (Rhône-Poulenc Rorer SA) *Polyhydroxyalkylpyrazine derivs., preparation and medicines containing them.* WO 9903842.

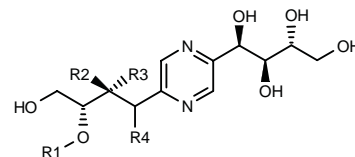
272824

(1*R*,2*S*,3*R*)-1-[5-[3(*S*),4-Dihydroxybutyl]-2-pyrazinyl]-1,2,3,4-butanetetraol

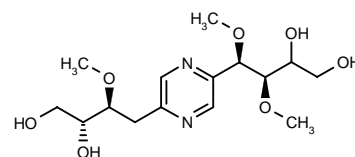


C₁₂ H₂₀ N₂ O₆; Mol wt: 288.2980

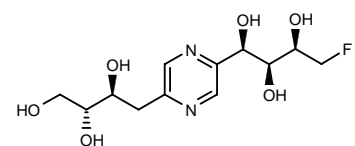
ACTION – Hypoglycemic agent whose activity was demonstrated *in vivo* in mice given an oral glucose load at doses of 3-50 mg/kg p.o. (at least 10% reduction in glycemia). LD₅₀ > 2000 mg/kg p.o. in mice. Other preferred compounds within this series of specifically claimed polyhydroxybutylpyrazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
272825	H	H	bond		C ₁₂ H ₁₈ N ₂ O ₆
272826	H	OMe	H	H	C ₁₃ H ₂₂ N ₂ O ₇
272827	H	H	F	H	C ₁₂ H ₁₉ FN ₂ O ₆
272828	Me	OH	H	H	C ₁₃ H ₂₂ N ₂ O ₇



272829: C₁₅ H₂₆ N₂ O₇



272830: C₁₂ H₁₉ F N₂ O₆

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Bashiardes, G. et al. (Rhône-Poulenc Rorer SA) *Polyhydroxybutylpyrazines, their preparation and medicines containing them.* WO 9903841.

ACTION – Colonic prokinetic agent, an ester-type prodrug of AU-130* that increases colonic activity through the activation of cholinergic neurons and 5-HT₄ receptors. In dogs, compound dose-dependently enhanced colonic motility and induced bowel contractions and defecation in the dose range of 0.03-0.3 i.v. and 1-10 mg/kg p.o. In rats, it accelerated colonic transit and fecal pellet output at 1-10 mg/kg p.o. Compound did not induce watery diarrhea in either species. The effects of AU-244 were completely inhibited in dogs by pretreatment with atropine, the 5-HT₄ receptor antagonist SB-207266 but not the 5-HT₃ receptor antagonist granisetron.

SOURCE – Hokuriku.

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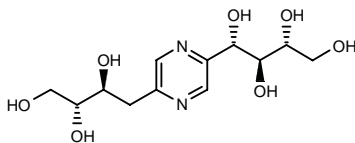
*Drug Data Rep 1998, 020(09): 0780.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

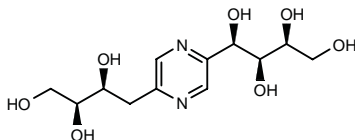
272809

(1*S*,2*S*,3*R*)-1-[5-[(2*S*,3*R*)-2,3,4-Trihydroxybutyl]-2-pyrazinyl]-1,2,3,4-butanetetraol

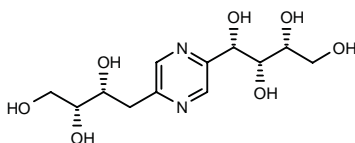


C₁₂ H₂₀ N₂ O₇; Mol wt: 304.2970

ACTION – Hypoglycemic agent, as demonstrated in mice with glycemia induced by an oral glucose load administered doses of 3-50 mg/kg p.o. It has low acute toxicity (LD₅₀ > 2000 mg/kg p.o.) in mice. Within this series of specifically claimed polyhydroxyalkylpyrazine derivatives, the following are also included:



272814: C₁₂ H₂₀ N₂ O₇



272815: C₁₂ H₂₀ N₂ O₇

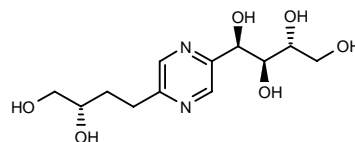
SOURCE – Rhône-Poulenc Rorer.

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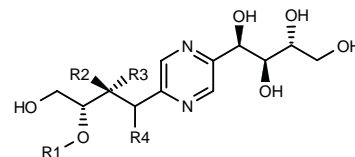
272824

(1*R*,2*S*,3*R*)-1-[5-[3(*S*),4-Dihydroxybutyl]-2-pyrazinyl]-1,2,3,4-butanetetraol

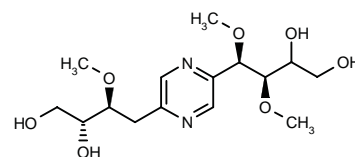


C₁₂ H₂₀ N₂ O₆; Mol wt: 288.2980

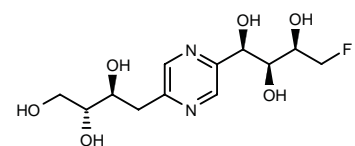
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Compound	R1	R2	R3	R4	Formula
272825	H	H	bond		C ₁₂ H ₁₈ N ₂ O ₆
272826	H	OMe	H	H	C ₁₃ H ₂₂ N ₂ O ₇
272827	H	H	F	H	C ₁₂ H ₁₉ FN ₂ O ₆
272828	Me	OH	H	H	C ₁₃ H ₂₂ N ₂ O ₇



272829: C₁₅ H₂₆ N₂ O₇



272830: C₁₂ H₁₉ F N₂ O₆

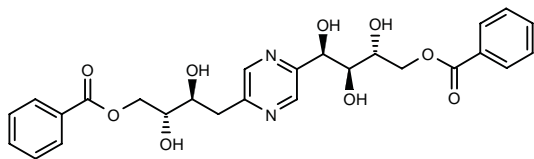
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Bashiardes, G. et al. (Rhône-Poulenc Rorer SA) *Polyhydroxybutylpyrazines, their preparation and medicines containing them.* WO 9903841.

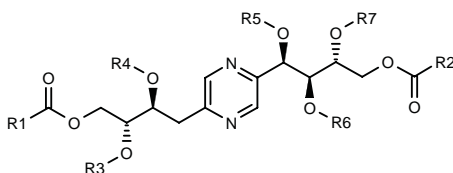
272837

Benzoic acid (2*R*,3*S*,4*R*)-4-[5-[(2*S*,3*R*)-4-(benzoyloxy)-2,3-dihydroxybutyl]-2-pyrazinyl]-2,3,4-trihydroxybutyl ester



C₂₆ H₂₈ N₂ O₉; Mol wt: 512.5122

ACTION – Hypoglycemic agent whose activity was assessed in mice given an oral glucose load and doses of 3-50 mg/kg p.o. (at least 10% reduction in glycemia). LD₅₀ > 2000 mg/kg p.o. in mice. Within this series of specifically claimed polyhydroxyalkylpyrazine derivatives, the following are also included:



Compound	R1=R2	R3=R4=R5=R6=R7	Formula
272838	Bu	H	C ₂₂ H ₃₆ N ₂ O ₉
272839	CH ₂ CH ₂ CO ₂ Me	COCH ₂ CH ₂ CO ₂ Me	C ₄₇ H ₆₂ N ₂ O ₂₈
272840	(CH ₂) ₃ CO ₂ H	CO(CH ₂) ₃ CO ₂ H	C ₄₆ H ₆₀ N ₂ O ₂₈
272841	2-thienyl	H	C ₂₂ H ₂₄ N ₂ O ₉ S ₂
272842	4-[(Pr) ₂ NCH ₂]-Ph	H	C ₄₀ H ₅₈ N ₄ O ₉

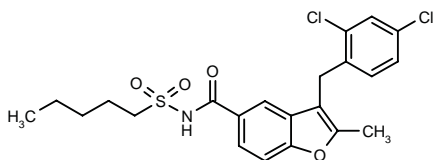
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Bouchard, H. et al. (Rhône-Poulenc Rorer SA) *Polyhydroxyalkylpyrazine derivs., preparation and medicines containing them*. WO 9903843.

273148

3-(2,4-Dichlorobenzyl)-2-methyl-*N*-(pentylsulfonyl)-benzofuran-5-carboxamide



C₂₂ H₂₃ Cl₂ N O₄ S; Mol wt: 468.3987

ACTION – Hypoglycemic agent proven to reduce blood glucose levels by 71% in *db/db* mice at 10 mg/kg p.o. administered in the diet twice a week for 2 weeks. Compound is also reported to possess cGMP-phosphodiesterase (cGMP-PDE)-inhibitory activity. A representative compound from a series of sulfonamide derivatives.

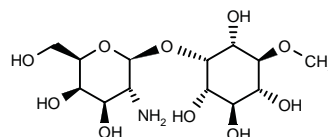
SOURCE – Fujisawa.

REFERENCES

1. Kayakiri, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Sulfonamide cpds. and medicinal use thereof*. WO 9900372.

273186

[1*S*-(1 α ,2 α ,3 β ,4 α ,5 β ,6 α)]-2-Amino-2-deoxy-1-*O*-(2,3,4,6-tetrahydroxy-5-methoxycyclohexyl)- β -D-galac-tose



C₁₃ H₂₅ N O₁₀; Mol wt: 355.3375

ACTION – Synthetic insulin mimetic for the treatment of disorders of glucose metabolism such as impaired glucose tolerance, elevated blood glucose associated with type II diabetes, and insulin resistance and physiological conditions associated therewith such as diabetes mellitus, obesity, hyperlipidemia, atherosclerosis and hypertension. *In vivo* in streptozotocin-diabetic rats, it reduced serum glucose levels by 30% at 2 mg/kg i.v. A representative compound from a series of small amino disaccharides.

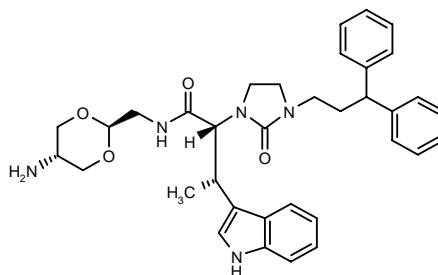
SOURCE – University of Virginia, Charlottesville, VA (US).

REFERENCES

1. Lerner, J. et al. (The University of Virginia Patent Foundation) *Synthetic insulin mimetic substances*. WO 9906421.

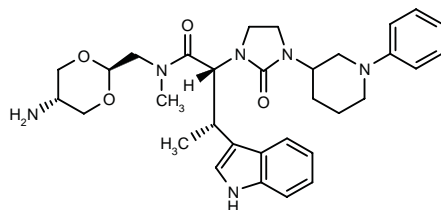
TREATMENT OF GROWTH HORMONE SECRETION DISORDERS**273035**

(2*R*,3*S*)-*N*-(*trans*-5-Amino-1,3-dioxan-2-ylmethyl)-3-(3-indolyl)-2-[3-(3,3-diphenylpropyl)-2-oxo-1-imidazol-idinyl]butanamide



C₃₅ H₄₁ N₅ O₄; Mol wt: 595.7399

ACTION – Potent somatostatin receptor agonist with high selectivity for the human sst2 subtype (K_i = 8.5 nM) over human sst3 and sst5 receptor subtypes (K_i = 8.4 and 1.1 μ M, respectively). It inhibited growth hormone release in an *in vitro* assay using primary cultures of rat anterior pituitary cells with an IC₅₀ of 70 nM, and it showed excellent oral bioavailability (67%) in dogs. Another related compound from this series of cyclic-urea based compounds is:



272689: C32 H42 N6 O4

SOURCE – Merck & Co.

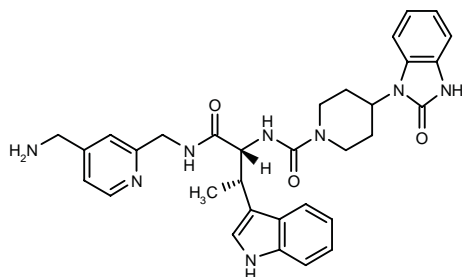
REFERENCES

1. Pasternak, A. et al. *Potent, orally bioavailable somatostatin agonists: Good absorption achieved by urea backbone cyclization.* Bioorg Med Chem Lett 1999, 9(3): 491.

L-054852

273786

N-[4-(Aminomethyl)-2-pyridinylmethyl]-2(*R*)-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-ylcarboxamido]-3(*S*)-methyl-3-(1*H*-indol-3-yl)propionamide



C32 H36 N8 O3; Mol wt: 580.6894

ACTION – Potent human somatostatin sst2 receptor agonist ($K_i = 0.06$ nM) with high selectivity over sst1, sst3, sst4 and sst5 receptors ($K_i = 4560, 391, 4600$ and 1120 nM, respectively), as well as other receptors. In *in vitro* functional studies, compound inhibited growth hormone release from rat pituitary cells with an IC_{50} of 0.05 nM. In *vivo* in *ob/ob* obese diabetic mice, compound reduced glucagon and glucose levels. Potentially useful for the treatment of acromegaly or diabetes.

SOURCE – Merck & Co.

REFERENCES

1. Yang, L. et al. (Merck & Co., Inc.) *Somatostatin agonists.* WO 9845285.
2. Yang, L. et al. *2,4-Bis(aminomethyl)pyridine derived highly potent and selective human somatostatin receptor subtype-2 (hsst2) agonists.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abstr MED1 141.

TROVERT™

253947

Pegylated human growth hormone mutein

B2036-PEG
G120K-PEG
Somavert

ACTION – Growth hormone (GH) receptor antagonist, a pegylated analogue of human GH that acts as a competitive antagonist, preventing receptor dimerization. It was able to normalize diabetic renal and glomerular hypertrophy after 1 month of treatment (2 mg/kg s.c. every second day) in streptozotocin-diabetic mice. Compound also reduced diabetes-associated urinary albumin excretion but did not affect metabolic control or blood levels of GH, IGF-I or IGFBP-3, indicating that its effects may be mediated by specific inhibition of renal IGF-I through the renal GH receptor. It is currently in phase III in patients with acromegaly and diabetes and it is also potentially useful for the treatment of diabetic kidney disease.

SOURCES – Genentech; Sensus.

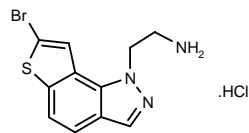
REFERENCES

1. Flyvbjerg, A. et al. *Effect of a long-acting growth hormone receptor antagonist (G120K-PEG) on renal enlargement, glomerular hypertrophy and urinary albumin excretion in experimental diabetes in mice.* Eur J Endocrinol 1998, 138(Suppl. 1): Abstr 10.
2. Flyvbjerg, A. et al. *Inhibitory effect of a growth hormone receptor antagonist (G120K-PEG) on renal enlargement, glomerular hypertrophy, and urinary albumin excretion in experimental diabetes in mice.* Diabetes 1999, 48(2): 377.
3. Khan, M.N. et al. *Development of a sensitive radioimmunoassay for the quantification of B2036-PEG in human serum: Validation and its application in a phase I study.* Pharm Res 1997, 14(11, Suppl.): Abstr 4160.
4. Maamra, M. et al. *The antagonist action of B2036 on growth hormone signalling is independent of receptor internalisation.* J Endocrinol 1999, 160(Suppl.): Abstr P168.
5. McCutcheon, I.E. et al. *The growth hormone receptor antagonist B2036PEG (Trovert) inhibits the growth of meningioma xenografts in nude mice.* Proc Amer Assoc Cancer Res 1999, 40 Abstr 4047.
6. Rodvold, K.A. et al. *Single-dose safety and pharmacokinetics of B2036-PEG (Somavert) after subcutaneous administration in healthy volunteers.* J Clin Pharmacol 1997, 37(9): Abstr 50.
7. Scarlet, J.A. *Growth hormone antagonists and insulin resistance.* IBC 2nd Int Conf Insulin Resist. Novel Drug Dev Strategies Type II Diabetes Obesity (Oct 6-7, Philadelphia) 1997.
8. Trainer, P.J. et al. *Successful treatment of acromegaly with a growth hormone receptor antagonist (Trovert™).* J Endocrinol 1998, 159(Suppl.): Abstr OC23.
9. Trainer, P.J. et al. *Modulation of cortisol metabolism by a growth hormone receptor antagonist (Trovert™) in patients with acromegaly.* J Endocrinol 1999, 160(Suppl.): Abstr OC33.
10. *Growth hormone antagonist enters phase II.* DailyDrugNews.com (Daily Essentials) 1997, Sept 18.
11. *Trovert receives Orphan Drug designation for acromegaly.* DailyDrugNews.com (Daily Essentials) 1997, Aug 13.

TREATMENT OF MALE SEXUAL DYSFUNCTION

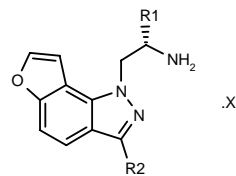
273800

2-(7-Bromo-1*H*-thieno[2,3-*g*]indazol-1-yl)ethylamine hydrochloride



C₁₁ H₁₀ Br N₃ S . HCl; Mol wt: 332.6519

ACTION – Agent for the treatment of CNS disorders such as sexual dysfunction, anxiety, depression, sleep disorders and eating disorders with preferential affinity for 5-HT_{2C} receptors relative to 5-HT_{2A} receptors, as demonstrated in a binding assay by K_i values of 0.8 and 18 nM, respectively. A representative compound from a series of tricyclic pyrrole and pyrazole derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
273801	Me	OMe	fumarate	C ₁₃ H ₁₅ N ₃ O ₂ ·C ₄ H ₄ O ₄
273802	H	Et	2HCl	C ₁₃ H ₁₆ N ₃ O ₂ ·2HCl

SOURCE – Yamanouchi.

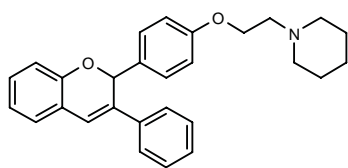
REFERENCES

1. Maeno, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Tricyclic pyrrole or pyrazole derivs.* WO 9856768.

CONTRACEPTIVES

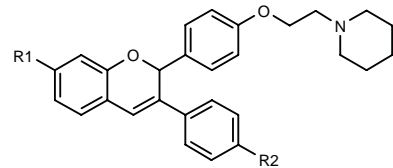
272512

(–)-3-Phenyl-2-[4-[2-(1-piperidinyloxy)phenyl]-2*H*-1-benzopyran



C₂₈ H₂₉ N O₂; Mol wt: 411.5421

ACTION – Nonsteroidal antiestrogenic agent, the (–)-enantiomer of CDRI-81/287⁺, useful for the treatment of estrogen-related diseases such as breast cancer, osteoporosis, hypercholesterolemia and endome-triosis, and particularly as a postcoital contraceptive. Other specifically claimed *dl*-2,3-diaryl-2*H*-1-benzopyran derivatives include the following:



Compound	R1	R2	Isomer	Formula
272513	H	OH	(–)	C ₂₈ H ₂₉ NO ₃
272514	OMe	H	(–)	C ₂₉ H ₃₁ NO ₃
272516	OH	OH	(–)	C ₂₈ H ₂₉ NO ₄
272517	H	OMe	(–)	C ₂₉ H ₃₁ NO ₃
272518	H	H	(+)	C ₂₈ H ₂₉ NO ₂
272519	H	OMe	(+)	C ₂₉ H ₃₁ NO ₃

SOURCES – Central Drug Research Institute, Lucknow (IN); Novo Nordisk.

REFERENCES

1. Hajela, K. et al. (Novo Nordisk A/S;Central Drug Research Institute) *dl*-2,3-diaryl-2*H*-1-benzopyrans. WO 9902512.

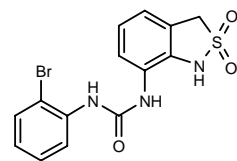
*Drug Data Rep 1992, 014(02): 0143.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

273322

N-(2-Bromophenyl)-*N*'-(2,2-dioxo-1,3-dihydro-2,1-benzisothiazol-7-yl)urea



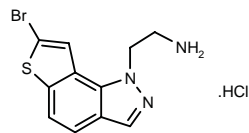
C₁₄ H₁₂ Br N₃ O₃ S; Mol wt: 382.2368

ACTION – Agent for the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, ulcerative colitis, septic shock, Alzheimer's disease and transplant rejection, a CXCR1 and/or CXCR2 receptor (formerly known as IL-8 receptors) antagonist. Other exemplified bicyclic compounds include the following:

TREATMENT OF MALE SEXUAL DYSFUNCTION

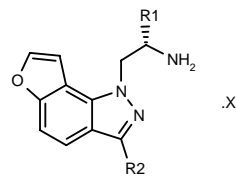
273800

2-(7-Bromo-1*H*-thieno[2,3-*g*]indazol-1-yl)ethylamine hydrochloride



C₁₁ H₁₀ Br N₃ S . HCl; Mol wt: 332.6519

ACTION – Agent for the treatment of CNS disorders such as sexual dysfunction, anxiety, depression, sleep disorders and eating disorders with preferential affinity for 5-HT_{2C} receptors relative to 5-HT_{2A} receptors, as demonstrated in a binding assay by K_i values of 0.8 and 18 nM, respectively. A representative compound from a series of tricyclic pyrrole and pyrazole derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
273801	Me	OMe	fumarate	C ₁₃ H ₁₅ N ₃ O ₂ ·C ₄ H ₄ O ₄
273802	H	Et	2HCl	C ₁₃ H ₁₆ N ₃ O ₂ ·2HCl

SOURCE – Yamanouchi.

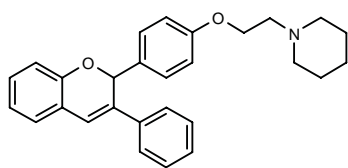
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1. Maeno, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Tricyclic pyrrole or pyrazole derivs.* WO 9856768.

CONTRACEPTIVES

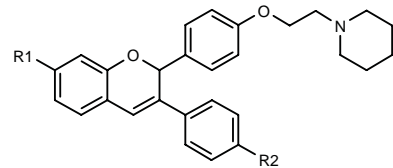
272512

(–)-3-Phenyl-2-[4-[2-(1-piperidinyloxy)phenyl]-2*H*-1-benzopyran



C₂₈ H₂₉ N O₂; Mol wt: 411.5421

ACTION – Nonsteroidal antiestrogenic agent, the (–)-enantiomer of CDRI-81/287⁺, useful for the treatment of estrogen-related diseases such as breast cancer, osteoporosis, hypercholesterolemia and endome-triosis, and particularly as a postcoital contraceptive. Other specifically claimed *dl*-2,3-diaryl-2*H*-1-benzopyran derivatives include the following:



Compound	R1	R2	Isomer	Formula
272513	H	OH	(–)	C ₂₈ H ₂₉ NO ₃
272514	OMe	H	(–)	C ₂₉ H ₃₁ NO ₃
272516	OH	OH	(–)	C ₂₈ H ₂₉ NO ₄
272517	H	OMe	(–)	C ₂₉ H ₃₁ NO ₃
272518	H	H	(+)	C ₂₈ H ₂₉ NO ₂
272519	H	OMe	(+)	C ₂₉ H ₃₁ NO ₃

SOURCES – Central Drug Research Institute, Lucknow (IN); Novo Nordisk.

REFERENCES

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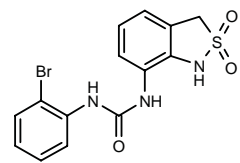
*Drug Data Rep 1992, 014(02): 0143.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

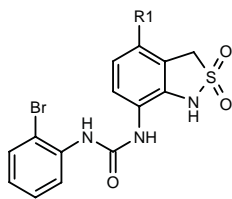
273322

N-(2-Bromophenyl)-*N*'-(2,2-dioxo-1,3-dihydro-2,1-benzisothiazol-7-yl)urea

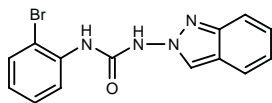


C₁₄ H₁₂ Br N₃ O₃ S; Mol wt: 382.2368

ACTION – Agent for the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, ulcerative colitis, septic shock, Alzheimer's disease and transplant rejection, a CXCR1 and/or CXCR2 receptor (formerly known as IL-8 receptors) antagonist. Other exemplified bicyclic compounds include the following:



Compound	R1	Formula
273323	F	C ₁₄ H ₁₁ BrFN ₃ O ₃ S
273324	Br	C ₁₄ H ₁₁ Br ₂ N ₃ O ₃ S



273325: C₁₄ H₁₁ Br N₄ O

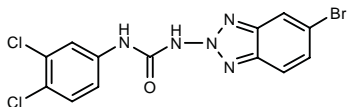
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Nie, H. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9832438.

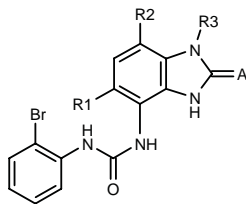
273326

N-(5-Bromo-2*H*-1,2,3-benzotriazol-2-yl)-*N'*-(3,4-dichlorophenyl)urea



C₁₃ H₈ Br Cl₂ N₅ O; Mol wt: 401.0502

ACTION – Agent for the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, ulcerative colitis, septic shock, Alzheimer's disease and transplant rejection, a CXCR1 and/or CXCR2 receptor (formerly known as IL-8 receptors) antagonist. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	A	Formula
273327	CN	H	Me	S	C ₁₆ H ₁₂ BrN ₅ OS
273328	H	CN	H	O	C ₁₅ H ₁₀ BrN ₅ O ₂
273329	H	CN	Me	O	C ₁₆ H ₁₂ BrN ₅ O ₂

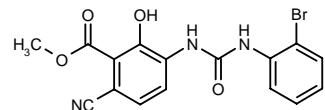
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Rutledge, M.C. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9832439.

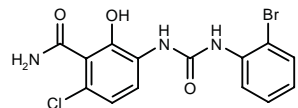
273911

3-[3-(2-Bromophenyl)ureido]-6-cyano-2-hydroxybenzoic acid methyl ester



C₁₆ H₁₂ Br N₃ O₄; Mol wt: 390.1918

ACTION – Chemokine CXCR2 receptor antagonist with more than 100-fold selectivity over CXCR1 receptors (IC₅₀ = 10.4 nM and 1.41 μM, respectively). Another related compound is:



273909: C₁₄ H₁₁ Br Cl N₃ O₃

Such compounds have been described as useful for the treatment of a wide variety of diseases including psoriasis, bronchial asthma, arthritis, inflammatory bowel disease, septic shock and Alzheimer's disease.

SOURCE – SmithKline Beecham.

REFERENCES

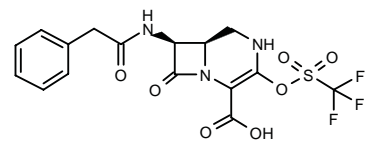
1. McClelland, B.W. et al. *Synthesis and characterization of potent CXCR2 antagonists containing an alkyl substituent adjacent to the phenol*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 206.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

270494

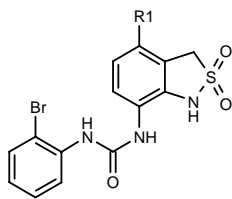
(±)-(6*S**,7*R**)-8-Oxo-7-(2-phenylacetamido)-3-(trifluoromethylsulfonyloxy)-1,4-diazabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



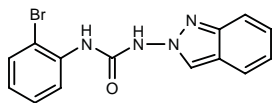
C₁₆ H₁₄ F₃ N₃ O₇ S; Mol wt: 449.3606

M.p. 100-2 °C.

ACTION – Isodethiazacephem antibiotic with strong activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (MIC = 0.010, 0.090, 0.68, 1.15 and 0.24 μg/ml, respectively); it was significantly more active than cefotaxime (MIC = 0.080, 0.25, 20.30, 62.35 and 10.25 μg/ml, respectively).



Compound	R1	Formula
273323	F	C ₁₄ H ₁₁ BrFN ₃ O ₃ S
273324	Br	C ₁₄ H ₁₁ Br ₂ N ₃ O ₃ S



273325: C₁₄ H₁₁ Br N₄ O

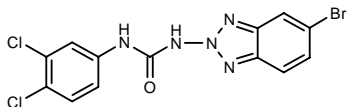
SOURCE – SmithKline Beecham.

REFERENCES

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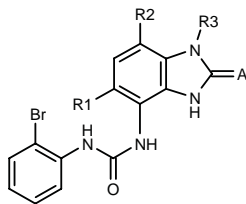
273326

N-(5-Bromo-2*H*-1,2,3-benzotriazol-2-yl)-*N'*-(3,4-dichlorophenyl)urea



C₁₃ H₈ Br Cl₂ N₅ O; Mol wt: 401.0502

ACTION – Agent for the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, ulcerative colitis, septic shock, Alzheimer's disease and transplant rejection, a CXCR1 and/or CXCR2 receptor (formerly known as IL-8 receptors) antagonist. Other exemplified bicyclic compounds include the following:



Compound	R1	R2	R3	A	Formula
273327	CN	H	Me	S	C ₁₆ H ₁₂ BrN ₅ OS
273328	H	CN	H	O	C ₁₅ H ₁₀ BrN ₅ O ₂
273329	H	CN	Me	O	C ₁₆ H ₁₂ BrN ₅ O ₂

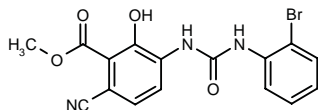
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Rutledge, M.C. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9832439.

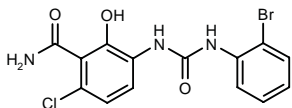
273911

3-[3-(2-Bromophenyl)ureido]-6-cyano-2-hydroxybenzoic acid methyl ester



C₁₆ H₁₂ Br N₃ O₄; Mol wt: 390.1918

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273909: C₁₄ H₁₁ Br Cl N₃ O₃

Such compounds have been described as useful for the treatment of a wide variety of diseases including psoriasis, bronchial asthma, arthritis, inflammatory bowel disease, septic shock and Alzheimer's disease.

SOURCE – SmithKline Beecham.

REFERENCES

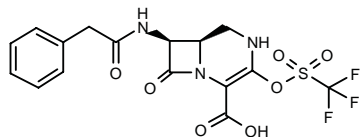
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

270494

(±)-(6*S**,7*R**)-8-Oxo-7-(2-phenylacetamido)-3-(trifluoromethylsulfonyloxy)-1,4-diazabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



C₁₆ H₁₄ F₃ N₃ O₇ S; Mol wt: 449.3606

M.p. 100-2 °C.

ACTION – Isodethiazacephem antibiotic with strong activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (MIC = 0.010, 0.090, 0.68, 1.15 and 0.24 μg/ml, respectively); it was significantly more active than cefotaxime (MIC = 0.080, 0.25, 20.30, 62.35 and 10.25 μg/ml, respectively).

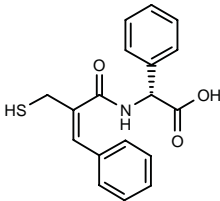
SOURCES – Academia Sinica, Taipei (TW); National Tsing Hua University, Hsinchu (TW).

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273168

2(*R*)-Phenyl-2-[3-phenyl-2-(sulfanylmethyl)-2(*E*)-propen-amido]acetic acid



C18 H17 N O3 S; Mol wt: 327.4023

ACTION – Agent for the treatment of bacterial infections when used in combination with a β -lactam antibiotic that acts by virtue of its metallo- β -lactamase-inhibitory activity ($I_{50} < 1 \mu\text{M}$ against the enzyme from *Bacteroides fragilis* CfiA). The MIC of meropenem alone against *B. fragilis* 262 was $> 128 \mu\text{g/ml}$ and the MIC of test compound alone was $> 256 \mu\text{g/ml}$; the MIC of meropenem in the presence of $8 \mu\text{g/ml}$ of test compound was reduced to $8 \mu\text{g/ml}$.

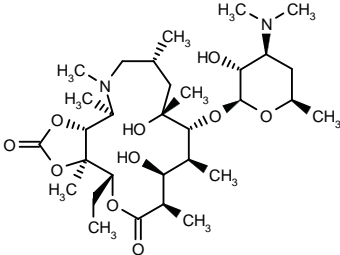
SOURCE – SmithKline Beecham.

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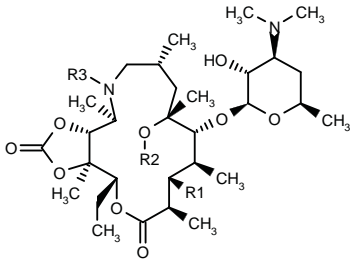
273312

9-Deoxo-3-des(hexopyranosyl)-9a-methyl-9a-aza-9a-homoerythromycin A 11-*O*,12-*O*-cyclic carbonate



C31 H56 N2 O10; Mol wt: 616.7874

ACTION – Azalide antibacterial agent active against Gram-positive and Gram-negative bacteria. A representative compound from a series of 9a-azalides, wherein the following are also specifically claimed:



Compound	R1	R2	R3	Formula
273313	OAc	-CH2-		C ₃₃ H ₅₆ N ₂ O ₁₁
273314	OCH2OCH2CH2OMe	-CH2-		C ₃₅ H ₆₂ N ₂ O ₁₂
273315	OCH2OMe	-CH2-		C ₃₃ H ₅₈ N ₂ O ₁₁
273316	OH	-CO-		C ₃₁ H ₅₂ N ₂ O ₁₁
273317	H	-CO-		C ₃₁ H ₅₂ N ₂ O ₁₀
273318	H	-CH2-		C ₃₁ H ₅₄ N ₂ O ₉
273319	OCS2Me	-CH2-		C ₃₃ H ₅₆ N ₂ O ₁₀ S ₂
273320	H	H	H	C ₃₀ H ₅₄ N ₂ O ₉
273321	H	H	Me	C ₃₁ H ₅₆ N ₂ O ₉

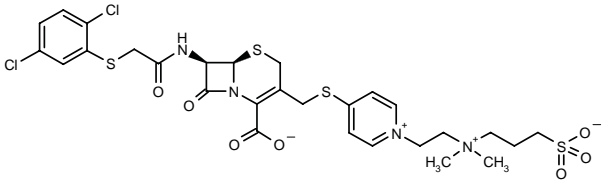
SOURCE – Merck & Co.

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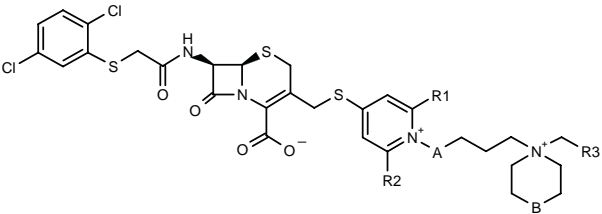
273590

(6*R*,7*R*)-7-[2-(2,5-Dichlorophenylsulfanyl)acetamido]-3-[1-[2-[*N,N*-dimethyl-*N*-(3-sulfonatopropyl)ammonio]ethyl]-pyridinio-4-ylsulfanylmethyl]-3-cephem-4-carboxylate

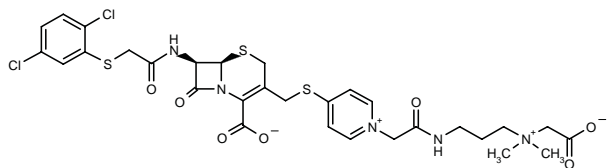


C28 H32 Cl2 N4 O7 S4; Mol wt: 735.7518

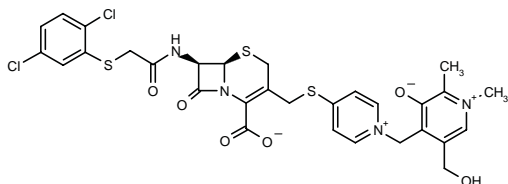
ACTION – Cephem antibiotic active against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA). Other specifically claimed compounds from this series of bis quaternary cephem derivatives include the following:



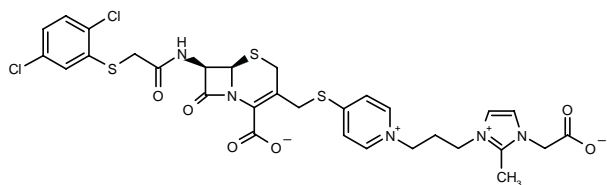
Compound	R1=R2	A	B	R3	Formula
273592	H	bond	-O-	CO ₂ ⁻	C ₃₀ H ₃₂ Cl ₂ N ₄ O ₇ S ₃
273593	Me	bond	-O-	CO ₂ ⁻	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₇ S ₃
273594	H	bond	-O-	CH ₂ CH ₂ SO ₃ ⁻	C ₃₁ H ₃₆ Cl ₂ N ₄ O ₈ S ₄
273595	H	-CH ₂ CONH-	-O-	CH ₂ CH ₂ SO ₃ ⁻	C ₃₃ H ₃₉ Cl ₂ N ₅ O ₉ S ₄
273596	H	bond	-CH(OH)-	CH ₂ CH ₂ SO ₃ ⁻	C ₃₂ H ₃₈ Cl ₂ N ₄ O ₈ S ₄



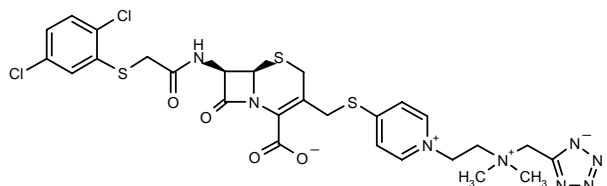
273591: C30 H33 Cl2 N5 O7 S3



273597: C30 H28 Cl2 N4 O6 S3



273598: C30 H29 Cl2 N5 O6 S3



273599: C27 H28 Cl2 N8 O4 S3

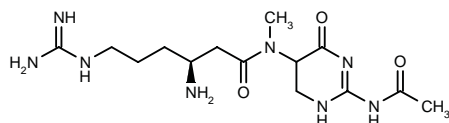
SOURCE – Bristol-Myers Squibb.

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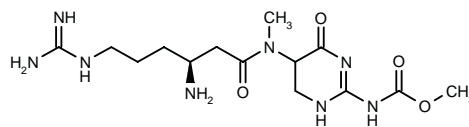
273622

N-[2-(Acetamido)-4-oxo-1,4,5,6-tetrahydropyrimidin-5-yl]-3(*S*)-amino-6-(guanidino)-*N*-methylhexanamide



C14 H26 N8 O3; Mol wt: 354.4124

ACTION – Antibiotic active *in vitro* against methicillin-resistant *Staphylococcus aureus* (MRSA) strains such as ATCC 33593 (methicillin-resistant and β -lactamase-positive; MIC = 8 μ g/ml). Also reported to possess antitumor activity. Another representative compound from this series of novel antibiotics is:



273623: C14 H26 N8 O4

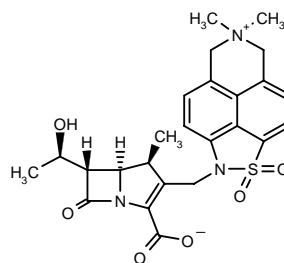
SOURCE – Research Corporation Technologies.

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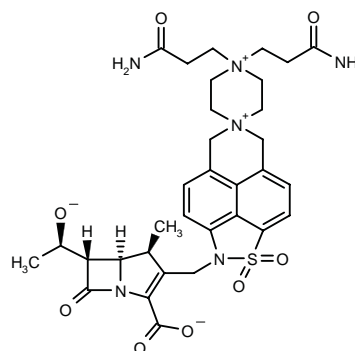
274007

(1*S*,5*R*,6*S*)-2-(6,6-Dimethyl-2,5,6,7-tetrahydro-[1,2]benzisothiazolo[5,4,3-*def*]isoquinolinium-2-ylmethyl)-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penam-3-carboxylate *S,S*-dioxide

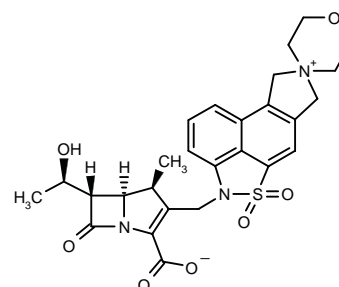


C25 H27 N3 O6 S; Mol wt: 497.5693

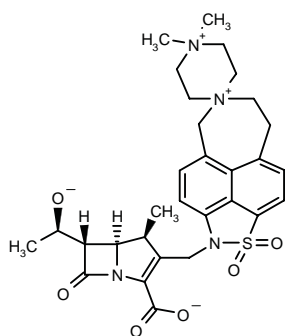
ACTION – Carbapenem antibiotic agent active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other specifically claimed compounds within this series of carbapenems substituted with a naphthosultam moiety include the following:



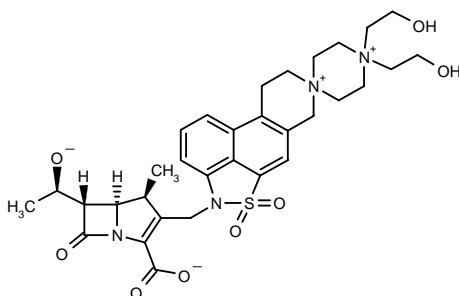
274009: C33 H40 N6 O8 S



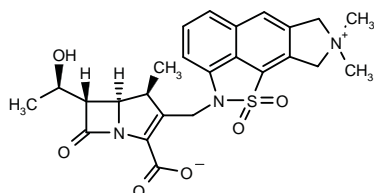
274011: C27 H29 N3 O7 S



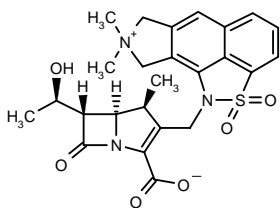
274012: C30 H36 N4 O6 S



274013: C32 H40 N4 O8 S



274015: C25 H27 N3 O6 S



274016: C25 H27 N3 O6 S

SOURCE – Merck & Co.

REFERENCES

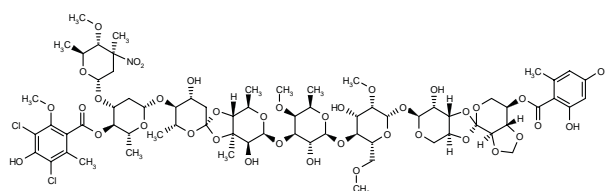
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Sch-27899

113569

O-[2,3,6-Trideoxy-3(*S*)-methyl-3-nitro- α -L-mannopyranosyl](1 \rightarrow 3)-O-[4-O-(3,5-dichloro-4-hydroxy-2,6-dimethylbenzoyl)-2,6-dideoxy- β -D-glucopyranosyl](1 \rightarrow 4)-O-(2,6-dideoxy-D-glucopyranosylidene)[1(*R*) \rightarrow 3,4]-O-(6-deoxy-3-C-methyl- β -D-mannopyranosyl)(1 \rightarrow 3)-O-(6-deoxy-4-O-methyl- β -D-galactopyranosyl)(1 \rightarrow 4)-O-(2,6-di-O-methyl- β -D-mannopyranosyl)(1 \rightarrow 1)-O-(α -L-lyxopyranosyl)-[3,4 \rightarrow 1(*R*)]-O-[4-O-(2,4-dihydroxy-6-methylbenzoyl)-2,3-O-methylene-D-arabinopyranose]

ZiracinTM



C70 H97 Cl2 N O38; Mol wt: 1631.4110

ACTION – Everninomicin glycopeptide antibiotic with excellent activity against multidrug-resistant Gram-positive pathogens including oxacillin- and erythromycin-resistant staphylococci, penicillin- and erythromycin-resistant streptococci and glycopeptide-resistant enterococci, with MIC values ranging from 0.008 to 0.5 μ g/ml. Compound was also active against a large variety of *Legionella* spp. with MIC values ranging from 0.008 to 0.25 μ g/ml. In a multicenter, randomized clinical study, compound (1-3 mg/kg/day i.v.) was as potent as ceftriaxone (2 mg/kg/day i.v.) against acute bacterial pneumonia due to *Streptococcus pneumoniae*. Currently undergoing phase III clinical trials.

SOURCE – Schering-Plough.

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SUBLANCIN 168

272864

ACTION – Highly stable antimicrobial peptide (lantibiotic) produced by *Bacillus subtilis* 168, proven to be particularly active against Gram-positive bacteria such as *Bacillus megaterium* No. 14581 and *B. subtilis* No. 6633 (MIC = 5 µg/ml).

SOURCE – University of Maryland, Baltimore, MD (US).

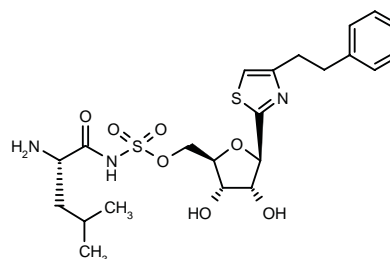
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ANTIBACTERIAL DRUGS

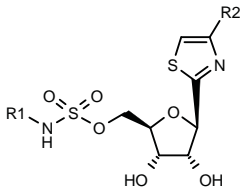
268007^{1,2}

N-(L-Leucyl)sulfamic acid 1-[4-(2-phenylethyl)thiazol-2-yl]-β-D-ribofuranos-5-*O*-yl ester



C22 H31 N3 O7 S2; Mol wt: 513.6329

ACTION – Antibacterial agent, an inhibitor of bacterial aminoacyl-tRNA synthetase with potent and selective activity against leucyl-tRNA synthetase from *Staphylococcus aureus* and *Escherichia coli* (IC₅₀ = 0.09 and < 0.002 µM, respectively) as compared to human enzyme (IC₅₀ = 0.73 µM). Other structurally related aminoacyl adenylate mimics include following:



Compound	R1	R2	Formula
268006	H-L-Leu	4-PhO-Ph	C ₂₆ H ₃₁ N ₃ O ₈ S ₂
268008	H-L-Leu	4-PhO-PhCH2CH2	C ₂₈ H ₃₅ N ₃ O ₈ S ₂
272675	H-L-Ile	Ph	C ₂₀ H ₂₇ N ₃ O ₇ S ₂

SOURCE – Cubist.

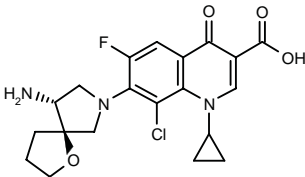
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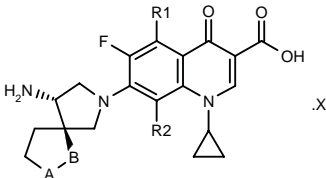
273243

7-[(5*R**,9*R**)-9-Amino-1-oxa-7-azaspiro[4.4]non-7-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C20 H21 Cl F N3 O4; Mol wt: 421.8539

ACTION – Quinolone antibacterial agent with potent activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P JC-1 (MIC = 0.003 µg/ml or less), MS16405 (MIC = 0.39 µg/ml) and 50774 (MIC = 0.003 or less), *Escherichia coli* NIHJ JC-2 and P-51208 strains (MIC = 0.006 and 0.2 µg/ml, respectively) and *Pseudomonas aeruginosa* No. 12 (MIC = 0.39 µg/ml). *In vivo*, compound showed good protection against murine infections caused by *S. aureus* 50774, giving ED₅₀ values of 0.78 and 2.21 mg/kg i.v. and p.o., respectively. Other compounds from this series of quinolone derivatives include the following:



p1025

271736

Ac-Gln-Leu-Lys-Thr-Ala-Asp-Leu-Pro-Ala-Gly-Arg-Asp-Glu-Thr-Thr-Ser-Phe-Val-Leu-Val-NH₂ acetate

C97 H160 N26 O32 . C2 H4 O2; Mol wt: 2262.5330

ACTION – Antimicrobial agent, a synthetic peptide adhesion epitope proven to inhibit the binding of a *Streptococcus mutans* cell-surface adhesin to salivary receptors *in vitro*, giving maximum inhibition of 70% at 100 µM. Direct application of the compound to the teeth in a streptococcal adhesion model in healthy volunteers prevented recolonization of *S. mutans* but not of Actinomyces, indicating the specificity of the compound; no side effects were observed and it appeared to be nonimmunogenic. Potentially useful for the prevention of microbial infections, such as in dental caries.

SOURCES – Actinova; United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, London (GB).

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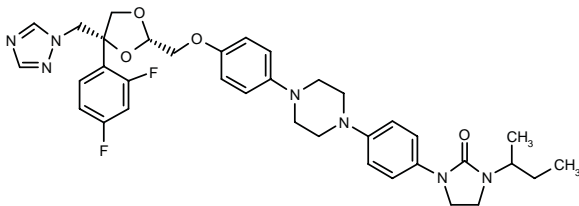
1. Kelly, C.G. et al. *A synthetic peptide adhesion epitope as a novel antimicrobial agent.* Nat Biotechnol 1999, 17(1): 42.

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ANTIFUNGAL AGENTS

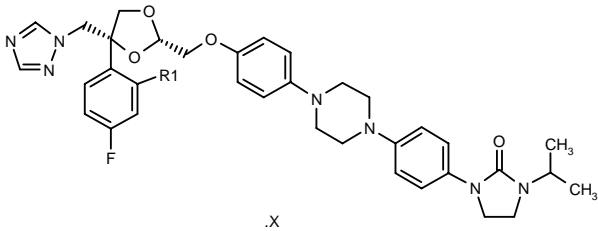
272536

(±)-*cis*-1-[4-[4-[4-[4-(2,4-Difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-ylmethoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylpropyl)imidazolidin-2-one



C36 H41 F2 N7 O4; Mol wt: 673.7609

ACTION – Antifungal agent active against *Candida kefyri* and *Trichophyton rubrum* (lowest active dose [LAD] = 0.1 µM or less). One of the most preferred compounds within a series of 2,4,4-trisubstituted-1,3-dioxolane derivatives, wherein the following are also included:



Compound	R1	X	Isomer	Formula
272537	H		cis	C ₃₅ H ₄₀ FN ₇ O ₄
272538	F		2 <i>S</i> ,4 <i>R</i>	C ₃₅ H ₃₈ F ₂ N ₇ O ₄
272539	F	2HCl	2 <i>S</i> ,4 <i>R</i>	C ₃₅ H ₃₈ F ₂ N ₇ O ₄ ·2HCl

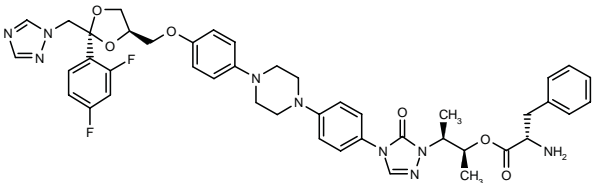
SOURCE – Janssen.

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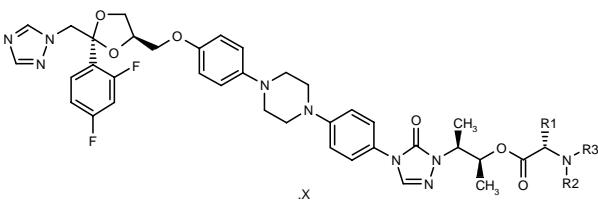
273224

L-Phenylalanine 2(*S*)-[4-[4-[4-[(2*S*,4*R*)-2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]-1-piperazinyl]phenyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-1(*S*)-methylpropyl ester



C44 H47 F2 N9 O6; Mol wt: 835.9083

ACTION – Orally active triazole antifungal agent with broad-spectrum activity against a variety of fungi, good aqueous solubility and high metabolic stability. *In vitro*, it was active against *Candida albicans* (MIC < 0.1 µM), *Candida krusei* (MIC = 1 µM), *Candida parapsilosis* (MIC < 0.1 µM), *Candida tropicalis* (MIC < 0.1 µM), *Microsporum canis* (MIC < 1 µM), *Trichophyton rubrum* (MIC < 0.1 µM), *Cryptococcus neoformans* (MIC = 1 µM) and *Aspergillus fumigatus* (MIC = 1 µM). *In vivo*, it was effective in guinea pig models of disseminated candidosis (83.3 and 100% survival, respectively, at 5 mg/kg/day i.v. and p.o.) and aspergillosis (83.3 and 30% survival, respectively, at 5 mg/kg/day i.v. and p.o.). Other exemplified compounds from this series of amino acid ester-containing azoles include the following:



Compound	R1	R2	R3	R4	Formula
273225	H	Et	Et	fumarate	C ₄₁ H ₄₉ F ₂ N ₉ O ₆ ·C ₄ H ₄ O ₄
273226	i-Pr	H	H		C ₄₀ H ₄₇ F ₂ N ₉ O ₆
273227	i-Bu	H	H		C ₄₁ H ₄₉ F ₂ N ₉ O ₆

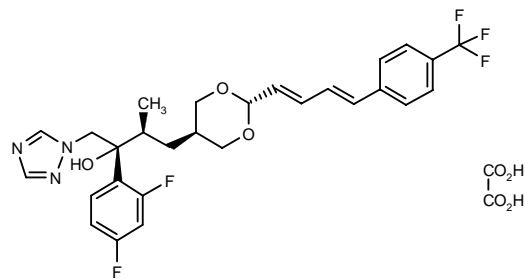
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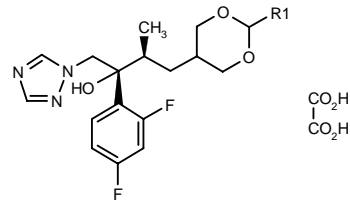
273267

trans-2-(*R*)-(2,4-Difluorophenyl)-3(*S*)-methyl-1-(1,2,4-triazol-1-yl)-4-[2-[4-[4-(trifluoromethyl)phenyl]-1(*E*),3(*E*)-butadienyl]-1,3-dioxan-5-yl]-2-butanol oxalate



C28 H28 F5 N3 O3 . C2 H2 O4; Mol wt: 639.5710

ACTION – Orally active antifungal agent with potent *in vitro* activity against *Candida albicans* SANK 51486 (MIC = 0.008 µg/ml or less) and *Aspergillus fumigatus* SANK 10569 (MIC = 0.063 µg/ml). *In vivo*, compound provided 100% protection against mortality in mice inoculated with *C. albicans* SANK 10569 at 14 and 21 days postinfection when given at 20 mg/kg p.o. at 1, 4 and 24 h after inoculation; at the same dose, fluconazole provided only 60-70% protection. Within this series of triazole derivatives, the following are also included:



Compound	R1	Formula
273268	4-CF3-Ph	C ₂₄ H ₂₄ F ₅ N ₃ O ₃ ·C ₂ H ₂ O ₄
273269	4-CF3-PhCH=CH	C ₂₆ H ₂₆ F ₅ N ₃ O ₃ ·C ₂ H ₂ O ₄
273270	4-CF3-Ph-CH=CHCH=CHCH=CH	C ₃₀ H ₃₀ F ₅ N ₃ O ₃ ·C ₂ H ₂ O ₄
273271	4-(CHF2CF2CH2O)-Ph-CH=CHCH=CH	C ₃₀ H ₃₁ F ₆ N ₃ O ₄ ·C ₂ H ₂ O ₄

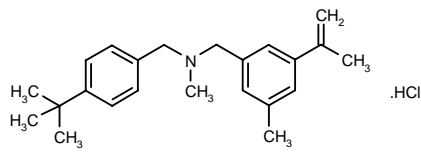
SOURCE – Sankyo.

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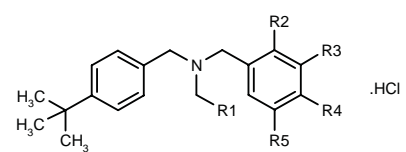
273822

N-(4-*tert*-Butylbenzyl)-*N*-(3-isopropenyl-5-methylbenzyl)-*N*-methylamine hydrochloride



C23 H31 N . HCl; Mol wt: 357.9658

ACTION – Antifungal agent with MIC values of 0.05, 0.05, 0.1, 0.1 and 0.05 µg/ml when tested *in vitro* against *Trichophyton mentagrophytes* IFO7552, *Trichophyton rubrum* IFO5808, *Trichophyton violaceum* TIMM1264, *Microsporum gypseum* IFO8231 and *Microsporum canis* TIMM0760. Other exemplified compounds from this series of substituted dibenzylamine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
273823	H	H	C(Me)=CH2	H	H	C ₂₂ H ₂₉ N.HCl
273826	H	H	vinyl	H	H	C ₂₁ H ₂₇ N.HCl
273828	H	H	C(Et)=CH2	H	H	C ₂₃ H ₃₁ N.HCl
273830	H	H	C(Me)=CHMe	H	H	C ₂₃ H ₃₁ N.HCl
273831	H	H	C(Me)=CH2	H	F	C ₂₂ H ₂₈ FN.HCl
273833	H	C(Me)=CH2	H	H	H	C ₂₂ H ₂₉ N.HCl
273836	Me	H	C(Me)=CH2	H	H	C ₂₃ H ₃₁ N.HCl
273839	H	H	C(Me)=CH2	Me	H	C ₂₃ H ₃₁ N.HCl

SOURCE – Pola Chemical.

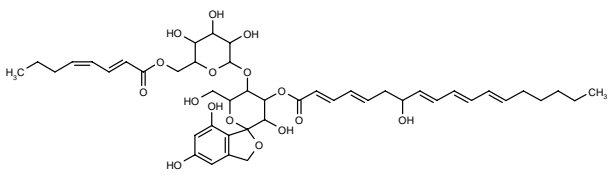
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AFA-0424

272835

7-Hydroxy-2(*E*),4(*E*),8(*E*),10(*E*),12(*E*)-octadecapentaenoic acid 3',5,7-trihydroxy-6'-(hydroxymethyl)-5'-[3,4,5-trihydroxy-6-[2(*E*),4(*Z*)-octadienoyloxy]tetrahydropyran-2-yloxy]spiro[isobenzofuran-1(3*H*),2'-tetrahydropyran]-4'-yl ester



C45 H60 O16; Mol wt: 856.9530

ACTION – Antifungal agent isolated from *Fusarium* TF-0547 (FERM P-16189), with potent *in vitro* activity against *Candida*, e.g., *Candida albicans* JCM1542 (MIC < 0.1 µg/ml) and *Candida tropicalis* YA-26002 (MIC = 0.2 µg/ml), with slightly higher potency than the reference compound amphotericin B (MIC = 0.39 and 0.78 µg/ml, respectively).

SOURCE – Taisho.

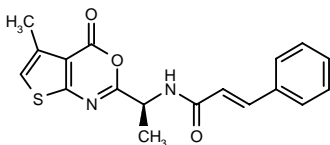
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ANTIVIRAL DRUGS

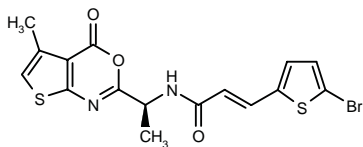
272677

N-[1(*S*)-(5-Methyl-4-oxo-4*H*-thieno[2,3-*d*][1,3]oxazin-2-yl)ethyl]-3-phenyl-2(*E*)-propenamide



C18 H16 N2 O3 S; Mol wt: 340.4014

ACTION – Antiviral agent, an inhibitor of herpesvirus proteases such as herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV) and cytomegalovirus (CMV) proteases (IC₅₀ = 0.3, 0.038 and 0.5 µM, respectively). Compound showed low cytotoxicity to MCR-5 cells (TC₅₀ = 56 µM in a cell culture assay; TC₅₀ > 250 µM in a pulse chase [PC] assay) and it inhibited viral protease processing in HSV-2-infected MCR-5 cells with a PC₅₀ of 7.5 µM using the PC assay. At up to 100 µM it was devoid of inhibitory activity against other serine proteases such as elastase and trypsin. Another compound from this series of thieno[2,3-*d*]oxazinones is:



272678: C16 H13 Br N2 O3 S2

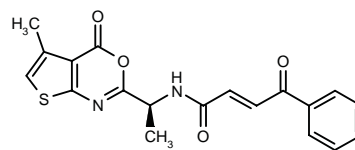
SOURCE – SmithKline Beecham.

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272679

N-[1(*S*)-(5-Methyl-4-oxo-4*H*-thieno[2,3-*d*][1,3]oxazin-2-yl)ethyl]-4-oxo-4-phenyl-2(*E*)-butenamide



C19 H16 N2 O4 S; Mol wt: 368.4114

ACTION – Potent inhibitor of human cytomegalovirus (HCMV) protease (IC₅₀ = 0.03 µM) with lower activity against varicella-zoster virus (VZV) and herpes simplex virus type 2 (HSV-2) proteases (IC₅₀ = 1 and 2.7 µM, respectively). However, it was highly cytotoxic to MRC-5 cells, with a TC₅₀ value of only 14 µM, precluding its further development as an antiviral agent for HCMV. Compound acts by acylating the catalytic serine of CMV protease and alkylating cysteine 161 via a Michael-type addition.

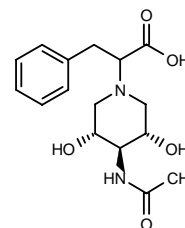
SOURCE – SmithKline Beecham.

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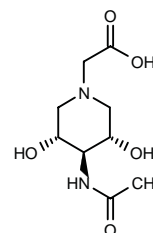
273169

(±)-2-[4(*R*)-Acetamido-3(*R*),5(*S*)-dihydroxy-1-piperidinyl]-3-phenylpropionic acid



C16 H22 N2 O5; Mol wt: 322.3588

ACTION – Antiviral and antibacterial agent that inhibits viruses such as influenza virus and bacterial pathogens such as *Salmonella*, *Vibrio* and *Clostridium*; it acts by inhibiting the enzyme neuraminidase. Another specifically claimed compound is:



273171: C9 H16 N2 O5

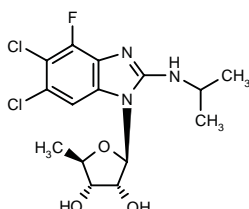
SOURCE – University of Florida, Gainesville, FL (US).

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273792

5,6-Dichloro-1-(5-deoxy-β-D-ribofuranosyl)-4-fluoro-*N*-isopropyl-1*H*-benzimidazol-2-amine



C15 H18 Cl2 F N3 O3; Mol wt: 378.2292

ACTION – Antiviral agent derived from 1263W94, active against human cytomegalovirus (HCMV); it inhibited HCMV replication with an IC_{50} of 0.34 μ M, with low cytotoxicity (32 μ M).

SOURCES – Glaxo Wellcome; University of Michigan, Ann Arbor, MI (US).

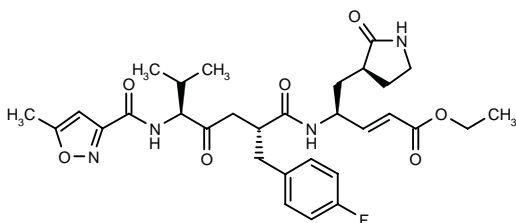
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AG-7088

268306

4(*S*)-[2(*R*)-(4-Fluorobenzyl)-6-methyl-5(*S*)-(5-methylisoxazol-3-ylcarboxamido)-4-oxoheptanamido]-5-[2-oxo-3(*S*)-pyrrolidinyl]-2(*E*)-pentenoic acid ethyl ester



C31 H39 F N4 O7; Mol wt: 598.6681

ACTION – Human rhinovirus (HRV) 3C protease inhibitor with potent and broad-spectrum antirhinoviral activity (EC_{90} = 0.02, 0.03 and 0.10 μ M, respectively, against serotypes 14, 2 and 10) and low cytotoxicity (CC_{50} > 100 μ M). Compound not only blocked rhinovirus replication, but also decreased levels of the inflammatory cytokines IL-6 and IL-8 in infected cells, indicating its potential to reduce clinical manifestations of infection. AG-7088 demonstrated good tolerability in phase I safety studies and was selected for clinical phase II trials.

SOURCE – Agouron.

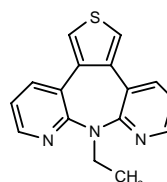
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AIDS MEDICINES

273159

8-Ethyl-8*H*-dipyrido[2,3-*b*:3,2'-*f*]thieno[3,4-*d*]azepine



C16 H13 N3 S; Mol wt: 279.3657

ACTION – Antiviral agent for AIDS with inhibitory activity against both wild-type HIV-1 and Y181C mutant reverse transcriptases (96 and 90% inhibition, respectively, of RNA-dependent DNA polymerase activity at 1 μ M). A representative compound from a series of dipyrido[2,3-*b*:3',2'-*f*]azepine derivatives.

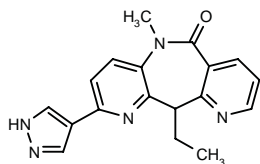
SOURCE – Boehringer Ingelheim.

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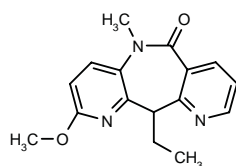
273161

11-Ethyl-5-methyl-2-(1*H*-pyrazol-4-yl)-6,11-dihydro-5*H*-dipyrido[3,2-*b*:2',3'-*e*]azepin-6-one



C18 H17 N5 O; Mol wt: 319.3663

ACTION – Antiviral agent for AIDS with the ability to inhibit both wild-type and mutant HIV-1 reverse transcriptase (80 and 56% inhibition of wild-type and Y181C, respectively, at 1 μ M). Another specifically claimed 5,11-dihydro-6*H*-dipyrido[3,2-*b*:2',3'-*e*]azepin-6-one derivative is:



273162: C16 H17 N3 O2

SOURCE – Boehringer Ingelheim.

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ALITRETINOIN

Prop INN

213594

9-*cis*-Retinoic acid

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

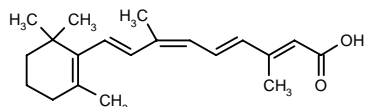
AGN-192013

ALRT-1057

LG-100057

LG-D1057⁺

NSC-659772



C20 H28 O2; Mol wt: 300.4450

M.p. 189 °C.

ACTION – Naturally occurring endogenous retinoid that binds to and activates all known intracellular retinoid receptor subtypes (RAR α , RAR β , RAR γ , RXR α , RXR β , RXR γ), which then function as transcription factors that regulate the expression of genes controlling the process of cellular differentiation and proliferation in both normal and neoplastic cells. The compound inhibits the growth of Kaposi's sarcoma cells *in vitro*.

INDICATION – Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.

PRESENTATION – Gel, 0.1% (w/w).

PROPRIETARY NAME – Panretin Gel (US).

SOURCE – Ligand.

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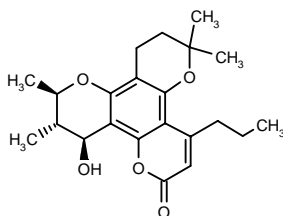
*Drug Data Rep 1994, 016(11): 1052.

(+)-DIHYDROCALANOLIDE A

273704

(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-propyl-7,8,11,12-tetrahydro-2*H*,6*H*,10*H*-benzo-[1,2-*b*:3,4-*b'*:5,6-*b''*]tripyran-2-one

NSC-678323



C22 H28 O5; Mol wt: 372.4582

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor. Compound showed a favorable pharmacokinetic profile, with enhanced bioavailability in comparison to (+)-calanolide A (46.8% and 13.2%, respectively). It is a candidate for further preclinical development and possible clinical evaluation as an oral agent for the treatment of HIV-1 infection.

SOURCE – National Cancer Institute, Bethesda, MD (US).

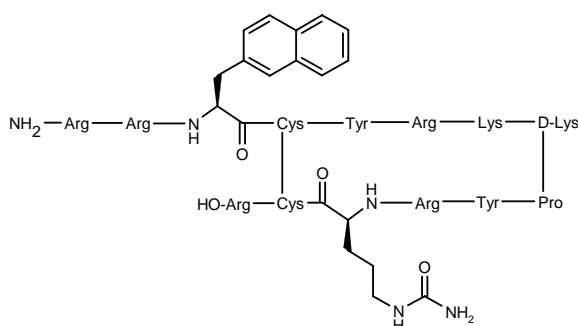
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- Newman, R.A. et al. *HPLC measurement of the novel non-nucleoside anti-HIV agent, (+) dihydrocalanolide A*. J Liq Chromatogr Relat Technol 1997, 20(4): 651.
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T-140

270244

Arginyl-arginyl-(2-naphthyl)alanyl-cysteinyl-tyrosyl-arginyl-lysyl-D-lysyl-prolyl-tyrosyl-arginyl-citrullinyl-cysteinyl-arginine cyclic (4-13)-disulfide



C90 H141 N33 O18 S2; Mol wt: 2037.4490

ACTION – Anti-HIV agent, a low-molecular-weight antagonist of the chemokine receptor CXCR4 that specifically inhibits HIV-1 entry mediated by CXCR4; it gave EC₅₀ values of 3.3-12 nM for inhibition of HIV-induced cytopathogenicity in MT-4 cells, with much lower cytotoxicity (CC₅₀ = 45-54 μM), and it inhibited viral antigen p24 expression with an EC₅₀ value of 0.023 nM.

SOURCE – Kyoto University, Kyoto (JP).

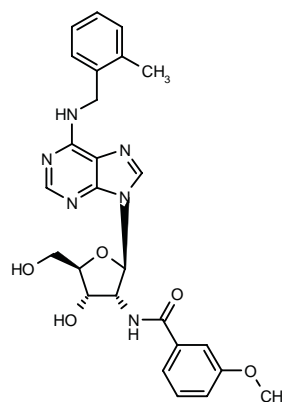
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TREATMENT OF PROTOZOAL DISEASES

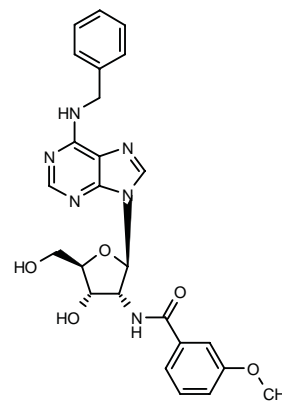
270504

2'-Deoxy-2'-(3-methoxybenzamido)-N⁶-(2-methylbenzyl)adenosine



C26 H28 N6 O5; Mol wt: 504.5442

ACTION – A potent and selective inhibitor of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) from *Leishmania mexicana*, *Trypanosoma cruzi* and *Trypanosoma brucei* (IC₅₀ = 4, 30, and 30 μM, respectively), whereas it did not inhibit human GAPDH at up to 270 μM. Based on its potency, selectivity and lipophilicity, compound is a promising antiparasitic drug candidate. Another adenosine analogue is:



270505: C25 H26 N6 O5

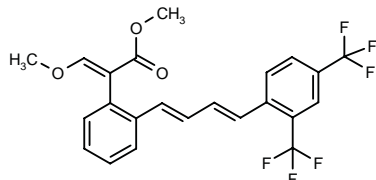
SOURCES – Howard Hughes Medical Institute, Chevy Chase, MD (US); University of Washington, Seattle, WA (US).

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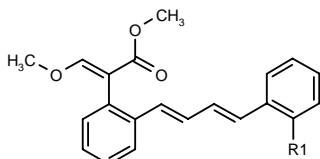
272546

2-[2-[4-[2,4-Bis(trifluoromethyl)phenyl]-1(*E*),3(*E*)-butadienyl]phenyl]-3-methoxy-2(*E*)-propenoic acid methyl ester



C23 H18 F6 O3; Mol wt: 456.3802

ACTION – Antimalarial agent active *in vitro* against the chloroquine-sensitive *Plasmodium falciparum* strain NF54 ($IC_{50} = 0.06 \mu\text{g/ml}$) and the chloroquine-resistant strain K1 ($IC_{50} = 0.13 \mu\text{g/ml}$). It was highly active *in vivo* in mice infected with *Plasmodium berghei* (100% reduction of parasitemia at 10 mg/kg p.o.). Within this series of β -alkoxyacrylate derivatives, the following are also included:



Compound	R1	Formula
272547	CF3	C ₂₂ H ₁₉ F ₃ O ₃
272548	Br	C ₂₁ H ₁₉ BrO ₃

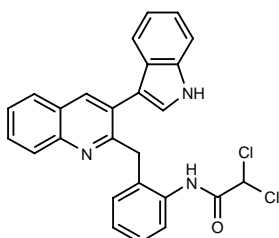
SOURCE – Roche.

REFERENCES

1. Alzeer, J. et al. (F. Hoffmann-La Roche AG) β -Alkoxyacrylates against malaria. WO 9902150.

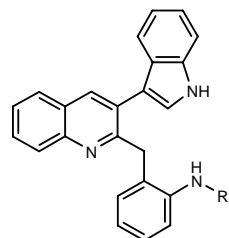
273667¹⁻³

2,2-Dichloro-*N*-[2-[3-(1*H*-indol-3-yl)-2-quinolinylmethyl]-phenyl]acetamide



C26 H19 Cl2 N3 O; Mol wt: 460.3621

ACTION – Antileishmanial agent, an indolylquinoline derivative active against *Leishmania donovani*; compound (5-10 mg/l) inhibited the growth of *L. donovani* promastigotes *in vitro* and eliminated amastigotes from infected peritoneal mouse macrophages. Compound exhibited no significant cytotoxicity in uninfected human peripheral blood mononuclear cells, and it was more efficacious than sodium antimony gluconate (SAG). In mice infected with *L. donovani*, compound was significantly more effective than SAG in reducing parasite load in the spleen (86% reduction at 12.5 mg/kg p.o. vs. 56% reduction at 250 mg/kg i.m.). Other related compounds are:



Compound	R1	Formula
273669 ^{1,2}	COCH2Cl	C ₂₆ H ₂₀ ClN ₃ O
273671 ^{1,2}	H	C ₂₄ H ₁₉ N ₃

SOURCE – Indian Institute of Chemical Biology, Calcutta (IN).

REFERENCES

1. Chakrabarti, G. et al. *Indolylquinoline derivatives are cytotoxic to Leishmania donovani promastigotes and amastigotes in vitro and are effective in treating murine visceral leishmaniasis*. J Antimicrob Chemother 1999, 43(3): 359.

2. Mahato, S.B. et al. *Synthesis of indolylquinolines under Friedel-Crafts reaction conditions*. Tetrahedron 1994, 50(36): 10803.

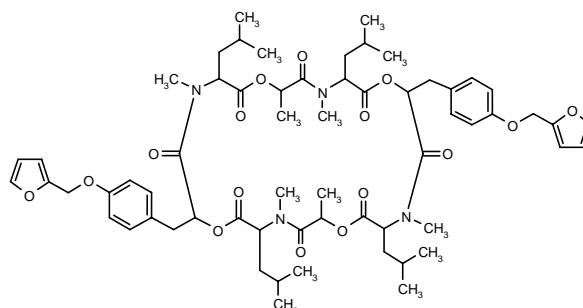
3. Ray, S. et al. *Dual inhibition of DNA topoisomerases of Leishmania donovani by novel indolyl quinolines*. Biochem Biophys Res Commun 1997, 230(1): 171.

TREATMENT OF HELMINTHIC DISEASES

PF1022-888

272730

6,18-Bis[4-(2-furylmethoxy)benzyl]-3,9,15,21-tetraiso-butyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,5,8,11,14,17,20,23-octaene



C62 H84 N4 O16; Mol wt: 1141.3580

ACTION – Anthelmintic agent, a novel cyclodepsipeptide derivative produced by culturing a filamentous fungus PF1022 strain (FERM BP-2671); it exhibits potent anthelmintic activity, particularly against organisms of the genus *Trichinella*. In *in vivo* studies, the compound exhibited a strong anthelmintic efficacy in mice infected with *Trichinella spiralis*, with complete elimination of the parasite at doses as low as 0.1 mg/kg i.p.

SOURCES – Bayer; Meiji Seika.

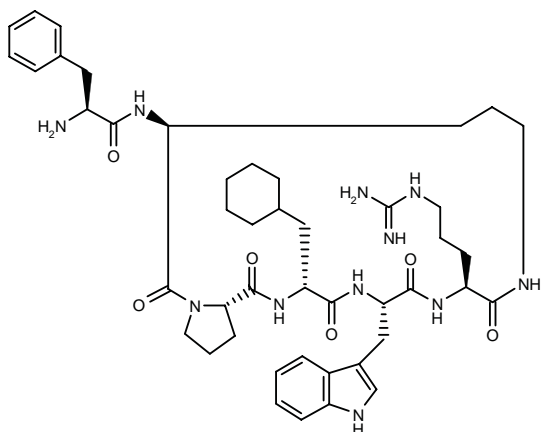
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TREATMENT OF SEPTIC SHOCK

272757

(3*S*,9*S*,12*S*,15*R*,18*S*)-15-(Cyclohexylmethyl)-9-(3-guanidinopropyl)-12-(1*H*-indol-3-ylmethyl)-3-(*L*-phenylalanyl-amino)-1,7,10,13,16-pentaazabicyclo[16.3.0]henicosane-2,8,11,14,17-pentaone



C45 H63 N11 O6; Mol wt: 854.0637

ACTION – Complement factor 5a (C5a) receptor antagonist with an apparent binding affinity of 27 nM against [¹²⁵I]-C5a in intact rat polymorphonuclear leukocytes (PMNs). In rats, compound given i.v. (0.3-10 mg/kg) dose-dependently inhibited the adherence of PMNs to the vascular endothelium, resulting in neutropenia, induced by either C5a or lipopolysaccharide (LPS). Potentially useful for reducing tissue damage in immunoinflammatory diseases such as sepsis.

SOURCE – University of Queensland, St. Lucia (AU).

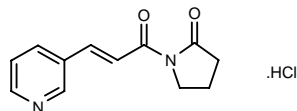
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1. Fairlie, D. et al. (University of Queensland) *Cyclic agonists and antagonists of C5a receptors and G protein-coupled receptors*. WO 9900406.
2. Short, A. et al. *Effects of a new C5a receptor antagonist on C5a- and endotoxin-induced neutropenia in the rat*. Br J Pharmacol 1999, 126(3): 551.

N-2733

273194

1-[3-(3-Pyridinyl)-2(*E*)-propenoyl]-2-pyrrolidinone hydrochloride



C12 H12 N2 O2 . HCl; Mol wt: 252.6997

ACTION – Antiinflammatory agent, a potent inhibitor of tumor necrosis factor (TNF- α) production (IC₅₀ = 11 μ M for inhibition of lipopolysaccharide [LPS]-induced release of TNF- α from THP-1 cells); compound did not affect cell viability at up to 100 μ M. *In vivo* in an LPS-induced murine endotoxic shock model, compound at doses of 100 mg/kg x 2 i.p. significantly decreased serum levels of TNF- α , and at doses of 30 and 100 mg/kg i.v. it restored the LPS-induced decrease in survival (30%) to 60 and 90%, respectively.

SOURCE – Nisshin Flour Milling.

REFERENCES

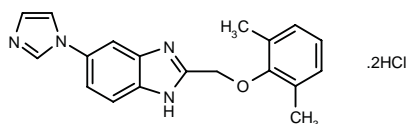
1. Hamaguchi, F. et al. (Nisshin Flour Milling Co., Ltd.) *Pyrrolidinone derivs*. JP 90225458.
2. Katsuyama, K. et al. (Nisshin Flour Milling Co., Ltd.) *Agents for inhibiting the production of IL-1 β and the release of TNF α* . CA 2165919, EP 720849, JP 96239322.
3. Katsuyama, K. et al. *N2733, 1-[3-(3-pyridyl)-acryloyl]-2-pyrrolidinone hydrochloride inhibits LPS-induced TNF- α production and improves survival in endotoxemic mice*. Biosci Biotechnol Biochem 1998, 62(11): 2177.
4. Nagasaka, T. et al. *Synthesis of 1-trans-cinnamoyl- and 1-[trans-3-(pyridyl)acryloyl]-2-pyrrolidinone derivatives and their effect on hemicholinium-induced impairment of water maze learning in mice*. Yakugaku Zasshi 1992, 112(2): 100.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

272290

2-(2,6-Dimethylphenoxyethyl)-5-(1*H*-imidazol-1-yl)-1*H*-benzimidazole dihydrochloride



C19 H18 N4 O . 2HCl; Mol wt: 391.3000

ACTION – Anthelmintic agent, a novel cyclodepsipeptide derivative produced by culturing a filamentous fungus PF1022 strain (FERM BP-2671); it exhibits potent anthelmintic activity, particularly against organisms of the genus *Trichinella*. In *in vivo* studies, the compound exhibited a strong anthelmintic efficacy in mice infected with *Trichinella spiralis*, with complete elimination of the parasite at doses as low as 0.1 mg/kg i.p.

SOURCES – Bayer; Meiji Seika.

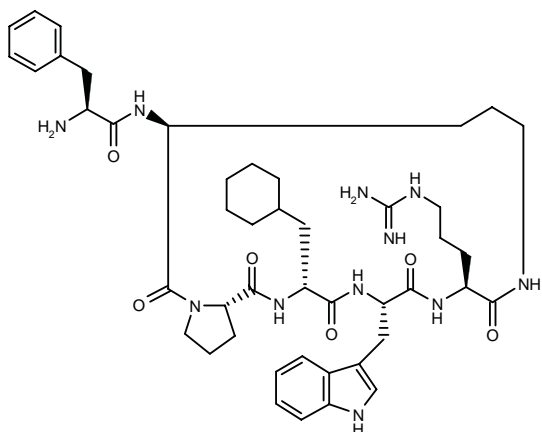
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TREATMENT OF SEPTIC SHOCK

272757

(3*S*,9*S*,12*S*,15*R*,18*S*)-15-(Cyclohexylmethyl)-9-(3-guanidinopropyl)-12-(1*H*-indol-3-ylmethyl)-3-(*L*-phenylalanyl-amino)-1,7,10,13,16-pentaazabicyclo[16.3.0]henicosane-2,8,11,14,17-pentaone



C45 H63 N11 O6; Mol wt: 854.0637

ACTION – Complement factor 5a (C5a) receptor antagonist with an apparent binding affinity of 27 nM against [¹²⁵I]-C5a in intact rat polymorphonuclear leukocytes (PMNs). In rats, compound given i.v. (0.3-10 mg/kg) dose-dependently inhibited the adherence of PMNs to the vascular endothelium, resulting in neutropenia, induced by either C5a or lipopolysaccharide (LPS). Potentially useful for reducing tissue damage in immunoinflammatory diseases such as sepsis.

SOURCE – University of Queensland, St. Lucia (AU).

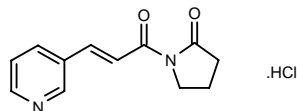
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2. Short, A. et al. *Effects of a new C5a receptor antagonist on C5a- and endotoxin-induced neutropenia in the rat*. Br J Pharmacol 1999, 126(3): 551.

N-2733

273194

1-[3-(3-Pyridinyl)-2(*E*)-propenoyl]-2-pyrrolidinone hydrochloride



C12 H12 N2 O2 . HCl; Mol wt: 252.6997

ACTION – Antiinflammatory agent, a potent inhibitor of tumor necrosis factor (TNF- α) production (IC₅₀ = 11 μ M for inhibition of lipopolysaccharide [LPS]-induced release of TNF- α from THP-1 cells); compound did not affect cell viability at up to 100 μ M. *In vivo* in an LPS-induced murine endotoxic shock model, compound at doses of 100 mg/kg x 2 i.p. significantly decreased serum levels of TNF- α , and at doses of 30 and 100 mg/kg i.v. it restored the LPS-induced decrease in survival (30%) to 60 and 90%, respectively.

SOURCE – Nisshin Flour Milling.

REFERENCES

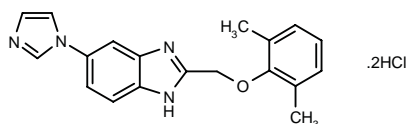
1. Hamaguchi, F. et al. (Nisshin Flour Milling Co., Ltd.) *Pyrrolidinone derivs*. JP 90225458.
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

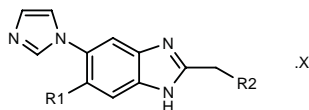
272290

2-(2,6-Dimethylphenoxyethyl)-5-(1*H*-imidazol-1-yl)-1*H*-benzimidazole dihydrochloride



C19 H18 N4 O . 2HCl; Mol wt: 391.3000

ACTION – Agent for the treatment of inflammatory disorders such as rheumatoid arthritis that acts by inhibiting IL-1 β activity and production. *In vivo*, compound was shown to inhibit tumor necrosis factor (TNF- α) production in a murine model of endotoxic shock induced by lipopolysaccharide, giving an ED₅₀ value of 3 mg/kg p.o. Other specifically claimed compounds from this series of benzimidazole, benzoxazole and benzothiazole derivatives include the following:



Compound	R1	R2	X	Formula
274149	H	OPh	2HCl	C ₁₇ H ₁₄ N ₄ O ₂ .2HCl
274151	H	SPh	2HCl	C ₁₇ H ₁₄ N ₄ S.2HCl
274153	H	2,6-(Me)2-PhS	2HCl	C ₁₈ H ₁₈ N ₄ S.2HCl
274155	H	NHSO2Ph	2HCl	C ₁₇ H ₁₅ N ₃ O ₂ S.2HCl
274157	4-F-Ph	2,6-(Me)2-Ph		C ₂₅ H ₂₁ N ₄ O

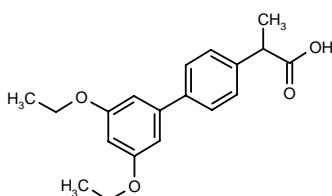
SOURCE – ADIR.

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1. De Nanteuil, G. et al. (ADIR et Cie.) *Benzimidazole, benzoxazole and benzothiazole derivs., their preparation and pharmaceutical compsns. containing them*. EP 894795, JP 99100368.

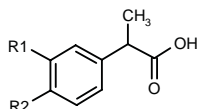
272666

2-(3',5'-Diethoxybiphenyl-4-yl)propionic acid



C₁₉ H₂₂ O₄; Mol wt: 314.3788

ACTION – Potent and selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.32 μ M) with 78-fold selectivity over COX-1 (IC₅₀ = 25 μ M); compound showed improved selectivity for COX-2 compared to DuP-697, but was at least 5-fold less selective than NS-398. Other related flurbiprofen analogues include the following:



Compound	R1	R2	Formula
272667	F	3,5-(EtO)2-Ph	C ₁₉ H ₂₁ FO ₄
272668	H	2-Me-1H-indol-5-yl	C ₁₈ H ₁₇ NO ₂

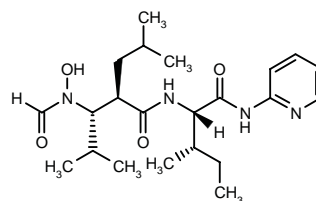
SOURCE – Merck Frosst.

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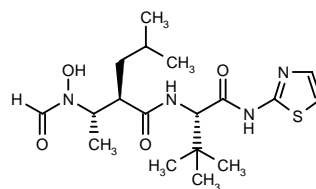
272734

N α -[3(*S*)-(N-Hydroxyformamido)-2(*R*)-isobutyl-4-methylpentanoyl]-*N*¹-(2-pyridyl)-L-isoleucylamide



C₂₂ H₃₆ N₄ O₄; Mol wt: 420.5504

ACTION – Agent for the treatment of rheumatoid arthritis, aberrant angiogenesis, tumor invasion and metastasis, an inhibitor of matrix metalloproteinases such as collagenase 1, collagenase 3, gelatinase B and stromelysin 1 (K_i < 100 nM) and of tumor necrosis factor- α (TNF- α) production, as demonstrated *in vitro* (IC₅₀ = 100-500 nM) and in serum of mice treated with lipopolysaccharide (> 75% inhibition at 40 mg/kg p.o.). Another specifically claimed reverse hydroxamate derivative is:



272735: C₁₈ H₃₀ N₄ O₄ S

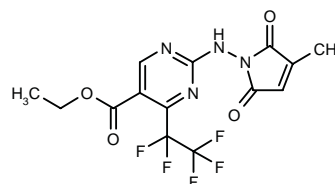
SOURCE – Glaxo Wellcome.

REFERENCES

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272736

2-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-ylamino)-4-(1,1,2,2,2-pentafluoroethyl)pyrimidine-5-carboxylic acid ethyl ester



C₁₄ H₁₁ F₅ N₄ O₄; Mol wt: 394.2549

ACTION – Agent for the treatment of immunoinflammatory and autoimmune diseases such as rheumatoid arthritis, osteoarthritis, transplant rejection, sepsis, adult respiratory distress syndrome (ARDS) and asthma that acts by inhibiting intracellular signal transduction and activating transcription factors, particularly NF- κ B and AP-1. Also reported to inhibit cytokine production. A representative compound within a series of specifically claimed pyrimidine derivatives.

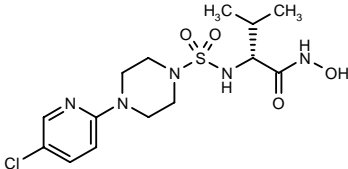
SOURCE – Signal.

REFERENCES

1. Suto, M.J. et al. (Signal Pharmaceuticals, Inc.) *Pyrimidine carboxylates and related cpds. and methods for treating inflammatory conditions.* WO 9838171.

272739

2(R)-[4-(5-Chloro-2-pyridinyl)-1-piperazinylsulfonamido]-N-hydroxy-3-methylbutyramide



C14 H22 Cl N5 O4 S; Mol wt: 391.8778

ACTION – Agent for the treatment of rheumatoid arthritis and osteoarthritis that acts as an inhibitor of matrix metalloproteinases such as collagenase 1 (IC₅₀ = 220 nM) and collagenase 3 (IC₅₀ = 1.3 nM). Compound was active in inhibiting collage matrix degradation both *in vitro* and *in vivo*. Certain compounds within the scope of the invention also inhibit the release of tumor necrosis factor (TNF) *in vitro* and *in vivo*.

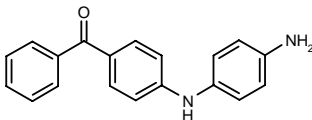
SOURCES – Agouron; Roche.

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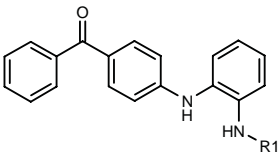
272745

4-(4-Aminophenylamino)benzophenone



C19 H16 N2 O; Mol wt: 288.3484

ACTION – Antiinflammatory and antiallergic agent, a potent inhibitor of IL-1β and tumor necrosis factor (TNF) production. *In vivo*, the compound exhibited activity comparable to hydrocortisone in inhibiting TPA-induced ear edema in mice, with the advantage of reduced side effects; it produced 40% inhibition of ear thickness and 76% inhibition of myeloperoxidase activity at 0.1 mg/ear (hydrocortisone: 58% and 69% inhibition, respectively, at the same dose). Potentially useful for the treatment of rheumatoid arthritis, asthma, gout, atherosclerosis, chronic inflammatory bowel disease, proliferative and inflammatory skin disorders such as psoriasis, and atopic dermatitis. Other representative compounds within this series of aminobenzophenone derivatives include the following:



Compound	R1	Formula
272746	H	C ₁₉ H ₁₆ N ₂ O
272748	4-Me-PhSO2	C ₂₆ H ₂₂ N ₂ O ₃ S

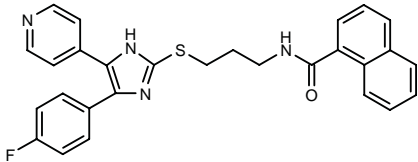
SOURCE – Leo.

REFERENCES

1. Ottosen, E.R. and Rachlin, S. (Leo Pharmaceutical Products Ltd. A/S) *Aminobenzophenones as inhibitors of interleukin and TNF.* WO 9832730.

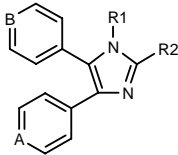
272865

N-[3-[4-(4-Fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-ylsulfanyl]propyl]-1-naphthalenecarboxamide



C28 H23 F N4 O S; Mol wt: 482.5807

ACTION – Antiinflammatory agent, a potent inhibitor of the production of inflammatory cytokines, particularly tumor necrosis factor (TNF-α; IC₅₀ = 97 nM in lipopolysaccharide [LPS]-stimulated peripheral blood mononuclear cells [PBMC]) and IL-1β (IC₅₀ = 86 nM in PBMCs stimulated by LPS), whose activity appears to be a consequence of its inhibitory activity on the enzyme p38 (or CSBP) kinase (IC₅₀ = 1.25 μM). Other specifically claimed 2-substituted imidazole derivatives include the following:



Compound	R1	R2	A	B	Formula
272866	H	CO(CH2)3OH	CF	N	C ₁₈ H ₁₆ FN ₃ O ₂
272868	1,3-dioxo-2-iso-indoliny-(CH2)3	CH2OH	CF	N	C ₂₆ H ₂₁ FN ₄ O ₃
272869	H	CH2SO2Pr	N	CF	C ₁₈ H ₁₈ FN ₃ O ₂ S

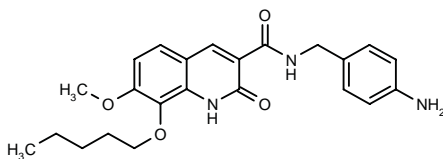
SOURCE – Ortho-McNeil.

REFERENCES

1. Wachter, M. and Beers, S.A. (Ortho-McNeil Pharmaceutical, Inc.) *2-Substd. imidazoles useful in the treatment of inflammatory diseases.* WO 9903837.

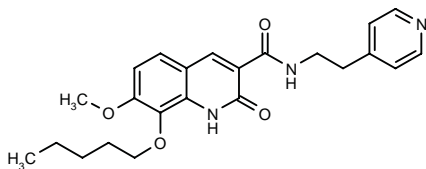
273112

N-(4-Aminobenzyl)-7-methoxy-2-oxo-8-(pentyloxy)-1,2-dihydroquinoline-3-carboxamide



C23 H27 N3 O4; Mol wt: 409.4833

ACTION – Agent for the treatment of immune and autoimmune diseases, inflammation, allergy and nephritis, a cannabinoid receptor ligand with selectivity for peripheral cannabinoid (CB₂) receptors over central cannabinoid (CB₁) receptors ($K_i < 0.4$ and 700 nM, respectively; ratio K_i CB₁/ K_i CB₂ > 1750) and which is reported to possess few CNS side effects. *In vivo*, compound exhibited potent antiinflammatory activity in the carrageenan-induced paw edema model in rats (ED₅₀ = 0.04 mg/kg p.o.). Another compound from this series of 2-oxo-1,2-dihydro-3-quinolinecarboxamides is:



273113: C23 H27 N3 O4

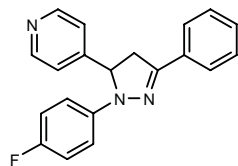
SOURCE – Japan Tobacco.

REFERENCES

1. Inaba, T. et al. (Japan Tobacco Inc.) *Quinoline cpds. and medicinal uses thereof*. JP 99080124, WO 9902499.

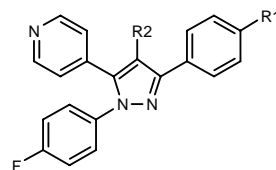
273195

4-[1-(4-Fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl]pyridine

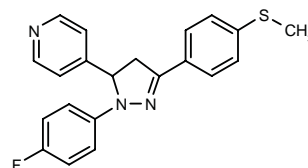


C20 H16 F N3; Mol wt: 317.3654

ACTION – An inhibitor of the production of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF) that acts by inhibiting p38 MAP kinase (also known as CSBP or RK kinase). Potentially useful in the treatment of a broad range of conditions including rheumatoid arthritis, osteoarthritis, septic shock, asthma, adult respiratory distress syndrome (ARDS), stroke, Alzheimer's disease, reperfusion injury, psoriasis, restenosis, osteoporosis, graft-versus-host disease, transplant rejection and ulcerative colitis. Within this series of pyrazole and pyrazoline derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
273196	H	H	C ₂₀ H ₁₄ FN ₃
273197	H	Br	C ₂₀ H ₁₃ BrFN ₃
273198	SMe	H	C ₂₁ H ₁₆ FN ₃ S
273199	SO ₂ Me	H	C ₂₁ H ₁₆ FN ₃ O ₂ S



275398: C21 H18 F N3 S

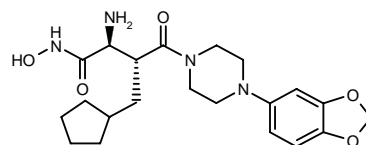
SOURCE – SmithKline Beecham.

REFERENCES

1. Adams, J.L. et al. (SmithKline Beecham Corp.) *Novel pyrazole and pyrazoline substd. cpds.* WO 9856377.

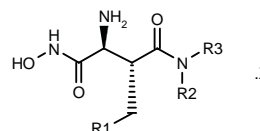
273330

(2*S*,3*R*)-2-Amino-4-[4-(1,3-benzodioxol-5-yl)-1-piperazinyl]-3-(cyclopentylmethyl)-4-oxobutyrohydroxamic acid



C21 H30 N4 O5; Mol wt: 418.4910

ACTION – A potent inhibitor of matrix metalloproteinases (MMPs) such as human collagenase (MMP-1; $K_i = 0.0065$ μM), human gelatinase A (MMP-2; $K_i = 0.02$ μM) and human stromelysin (MMP-3; $K_i = 0.24$ μM). Compound exhibited an oral bioavailability of 58 and 34%, respectively, in rats and cynomolgus monkeys at 15 mg/kg p.o. Potentially useful in the treatment of a broad range of disorders such as osteoarthritis, rheumatoid arthritis, osteoporosis, tumor metastasis, periodontitis, diabetic retinopathy, macular diseases, corneal, dermal or gastric ulceration, congestive heart failure and vascular restenosis. Other exemplified compounds include the following:



Compound	R1	R2	R3	X	Formula
273331	i-Pr		-CH ₂ CH ₂ OCH ₂ CH ₂ -		C ₁₂ H ₂₃ N ₃ O ₄
273332	cyclopentyl		-(CH ₂) ₅ -		C ₁₈ H ₂₇ N ₃ O ₃
273333	cyclopentyl	H	(R)-cyclohexyl-CH(Me)	CF ₃ CO ₂ H	C ₁₈ H ₃₃ N ₃ O ₃ ·C ₂ HF ₃ O ₂

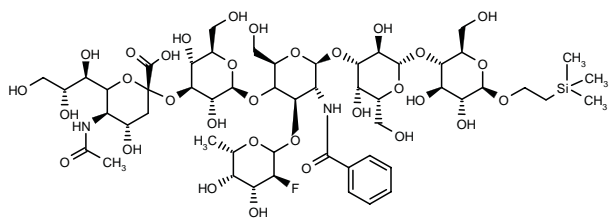
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Alpegiani, M. et al. (Pharmacia & Upjohn SpA) *Matrix metalloproteinase inhibitors*. WO 9902510.

273397

1-*O*-[2-(Trimethylsilyl)ethyl]-β-D-glucopyranosyl-(4→1)-*O*-(β-D-galactopyranosyl)-(3→1)-*O*-[2-benzamido-2-deoxy-3-*O*-(2-deoxy-2-fluoro-α-L-galactopyranosyl)-β-D-glucopyranosyl]-(4→1)-*O*-(β-D-galactopyranosyl)-(3→2)-*O*-neuraminic acid



C53 H85 F N2 O32 Si; Mol wt: 1309.3210

ACTION – Agent for the treatment or prevention of a broad range of inflammatory disorders, a sialyl Lewis X (SLe^x) derivative that inhibits selectin-mediated cellular adhesion and is reported to possess improved metabolic stability over structurally related compounds.

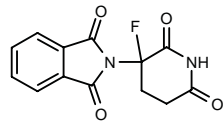
SOURCE – Daikin.

REFERENCES

1. Ohira, Y. and Iida, T. (Daikin Industries, Ltd.) *2-Fluorofucosyl-N-aroyleglucosamine derivs., intermediates therefor, and processes for producing these*. JP 99035593, WO 9903870.

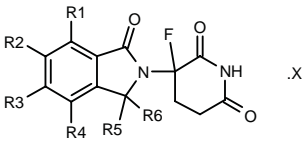
273409

2-(3-Fluoro-2,6-dioxo-3-piperidinyl)isoindoline-1,3-dione



C13 H9 F N2 O4; Mol wt: 276.2221

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, septic shock, graft-versus-host disease, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus and AIDS that acts by inhibiting tumor necrosis factor-α (TNF-α) production, NF-κB activation and/or phosphodiesterase activity. A compound within a series of substituted 1-oxo- and 1,3-dioxo-isoindolines, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
273410	H	H	H	H	H	H		C ₁₃ H ₁₁ FN ₂ O ₃
273411	F	F	F	F	-O-			C ₁₃ H ₅ F ₅ N ₂ O ₄
273412	H	H	NH2	H	H	H		C ₁₃ H ₁₂ FN ₃ O ₃
273413	H	NH2	H	H	-O-		HCl	C ₁₃ H ₁₀ FN ₃ O ₄ ·HCl

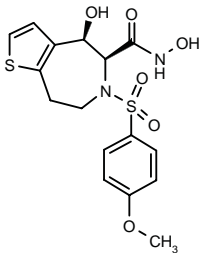
SOURCE – Celgene.

REFERENCES

1. Muller, G.W. et al. (Celgene Corp.) *Substd. 2-(2,6-dioxo-3-fluoropiperidin-3-yl)-isoindolines and method of reducing TNFα levels*. US 5874448.

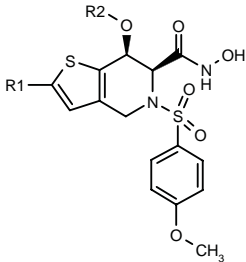
273477

cis-4-Hydroxy-6-(4-methoxyphenylsulfonyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine-5-carboxydroxamic acid

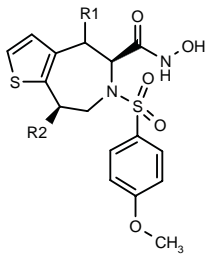


C16 H18 N2 O6 S2; Mol wt: 398.4582

ACTION – Agent for the treatment of inflammatory states such as arthritis and other tissue degradation disorders, an inhibitor of matrix metalloproteinases such as human neutrophil collagenase and/or human fibroblast stromelysin with IC₅₀ values of < 1 μM; also reported to inhibit the production of tumor necrosis factor (TNF-α) by monocytes following lipopolysaccharide (LPS) stimulation Within this series of hydroxamic acid-based compounds, the following are also included:



Compound	R1	R2	Formula
273479	H	H	C ₁₅ H ₁₆ N ₂ O ₆ S ₂
273481	3-Pyr	H	C ₂₀ H ₁₉ N ₃ O ₆ S ₂
273483	H	4-MeO-PhNHCO	C ₂₃ H ₂₃ N ₃ O ₈ S ₂
273484	H	4-Cl-PhNHCO	C ₂₂ H ₂₀ ClN ₃ O ₇ S ₂



Compound	R1	R2	Isomer	Formula
273482	CH2Ph	OH	5S*,8R*	C ₂₃ H ₂₄ N ₂ O ₆ S ₂
273485	CH2CH2Ph	H	trans	C ₂₄ H ₂₆ N ₂ O ₅ S ₂

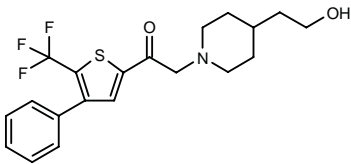
SOURCE – Amgen.

REFERENCES

1. Thomson, D.S. et al. (Amgen Inc.) *Hydroxamic acid substd. fused heterocyclic metalloproteinase inhibitors*. WO 9906410.

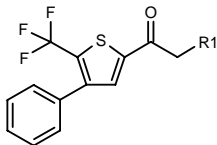
273763

2-[4-(2-Hydroxyethyl)-1-piperidiny]-1-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1-ethanone



C20 H22 F3 N O2 S; Mol wt: 397.4588

ACTION – Antiinflammatory agent found to inhibit IL-1β and tumor necrosis factor (TNF-α)-stimulated ICAM-1 production in vascular endothelial cells (IC₅₀ = 4 and < 1 μM, respectively). Other exemplified compounds within this series of thiophene derivatives include the following:



Compound	R1	Formula
273764	1-Piz	C ₁₇ H ₁₇ F ₃ N ₂ OS
273765	4-Me-1-Piz	C ₁₈ H ₁₉ F ₃ N ₂ OS
273766	4-(2-pyrimidinyl)-1-Piz	C ₂₁ H ₁₉ F ₃ N ₄ OS
273767	4-thiomorpholinyl	C ₁₇ H ₁₆ F ₃ NOS ₂
273768	1-Pip	C ₁₈ H ₁₈ F ₃ NOS
273769	4-OH-1-Pip	C ₁₈ H ₁₈ F ₃ NO ₂ S
273770	4-MeO-1-Pip	C ₁₉ H ₂₀ F ₃ NO ₂ S
273772	4-(ethynyl-CH2O)-1-Pip	C ₂₁ H ₂₀ F ₃ NO ₂ S
273773	4-EtO-1-Pip	C ₂₀ H ₂₂ F ₃ NO ₂ S
273774	3-(CH2OH)-1-Pip	C ₁₉ H ₂₀ F ₃ NO ₂ S
273776	3-thiazolidinyl	C ₁₆ H ₁₄ F ₃ NOS ₂
273778	2-CO2Me-4-OH-1-pyrrolidinyl	C ₁₉ H ₁₈ F ₃ NO ₄ S

SOURCE –Nippon Steel.

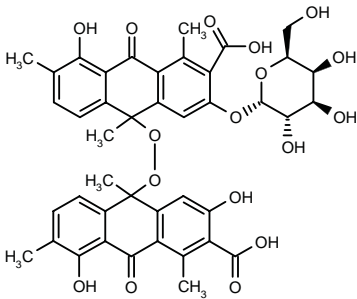
REFERENCES

1. Asari, T. et al. (Nippon Steel Corp.) *Novel anti-inflammatory agents*. JP 98316673.

ADXANTHROMYCIN

273092

10-(3-Carboxy-2,5-dihydroxy-4,6,9-trimethyl-10-oxo-9,10-dihydroanthracen-9-ylidioxo)-3-(α-L-galactopyranosyloxy)-8-hydroxy-1,7,10-trimethyl-9-oxo-9,10-dihydroanthracene-2-carboxylic acid



C42 H40 O17; Mol wt: 816.7610

Pale yellow powder, m.p. 233-5 °C (decomp.), [α]_D +120.5° (c 0.20, DMSO).

ACTION – An inhibitor of ICAM-1/LFA-1 (intracellular adhesion molecule-1/lymphocyte function-associated antigen-1)-mediated cell adhesion isolated from a culture broth of *Streptomyces* sp. NA-148. Compound inhibited the formation of JY Epstein-Barr virus-transformed B-lymphoblastoid cell aggregates at concentrations (1.5 μg/ml) lower than those exhibiting cytotoxicity (IC₅₀ = 15.2 μg/ml). Compound inhibited SKW-3 T-cell leukemia adhesion to soluble ICAM-1 with an IC₅₀ of 18.8 μg/ml, with cytotoxicity against SKW-3 cells at concentrations at least 5-fold higher (IC₅₀ = 110 μg/ml). Potentially useful for the treatment of inflammatory and immunological diseases.

SOURCES – Daiichi Pharmaceutical; Institute of Physical and Chemical Research (RIKEN), Saitama (JP); Teikyo University, Utsunomiya (JP).

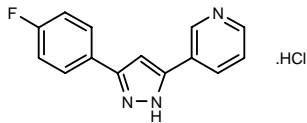
REFERENCES

1. Koiwa, T. et al. *Adxanthromycin: A new inhibitor of ICAM-1/LFA-1 mediated cell adhesion from Streptomyces sp. NA-148*. J Antibiot 1999, 52(2): 198.

IMMUNOMODULATING AGENTS

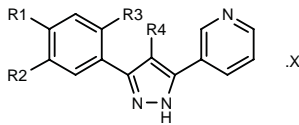
273359

3-[3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl]pyridine hydrochloride



C14 H10 F N3 . HCl; Mol wt: 275.7129

ACTION – Immunosuppressive agent proven to significantly inhibit collagen-induced arthritis in mice at a dose of 50 mg/kg/day p.o. x 7 days. Within this series of pyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
273360	Cl	H	-CH2-			C ₁₅ H ₁₀ ClN ₃
273362	Cl	H	-CH2-		HCl	C ₁₅ H ₁₀ ClN ₃ .HCl
273363	OMe	H	-(CH2)2-			C ₁₇ H ₁₅ N ₃ O
273365	Cl	H	H	H		C ₁₄ H ₁₀ ClN ₃
273367	OMe	F	H	H		C ₁₅ H ₁₂ FN ₃ O
273368	F	Br	H	H		C ₁₄ H ₉ BrFN ₃

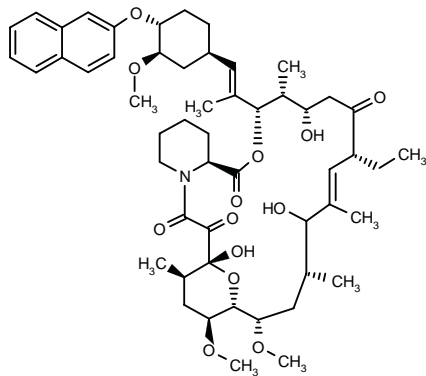
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Nakatsuka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrazole derivs.* WO 9856785.

273923

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14,20-trihydroxy-23,25-dimethoxy-12-[2-[3-methoxy-4-(2-naphthalenyloxy)cyclohexyl]-1(*E*)-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone



C53 H75 N O13; Mol wt: 934.1695

ACTION – Immunosuppressive macrolide with potential in the treatment of autoimmune diseases, infectious diseases and for the prevention of transplant rejection.

SOURCE – Merck & Co.

REFERENCES

1. Sinclair, P.J. (Merck & Co., Inc.) *Macrolides having immunosuppressive activity.* US 5877184.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

BUSULFAN

New formulation

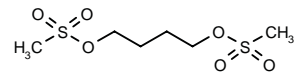
Rec INN; JAN; USAN

231560

1,4-Butanediol dimethanesulfonate

1,4-Bis(methanesulfonyloxy)butane

Busulphan (BAN)
NSC-750



C6 H14 O6 S2; Mol wt: 246.3026

ACTION – Antineoplastic agent, a bifunctional alkylating agent.

INDICATION – For use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

PRESENTATION – Single-use ampules (10 ml) for i.v. administration, 6 mg/ml.

PROPRIETARY NAME – *Busulfex* (US).

SOURCE – Orphan Medical.

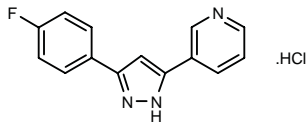
REFERENCES

- Andersson, B.S. et al. *Iv busulfan, cyclophosphamide (BuCy) and allogeneic hemopoietic stem cells (BMT) for chronic myeloid leukemia (CML).* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1168.
- Andersson, B.S. et al. *Parenteral busulfan/cyclophosphamide (BuCy) with allogeneic stem cell transplantation (PBPC) for advanced hematologic malignancies.* Proc Amer Soc Clin Oncol 1998, 17: Abst 292.
- Asai, O. et al. *Adding busulfan with cyclophosphamide - total body irradiation as preparative regimen for allogeneic transplantation reduced relapse rate in meyloid leukemia.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 999.
- Bertz, H. et al. *Busulfan/cyclophosphamide in volunteer unrelated donor (VUD) BMT: Excellent feasibility and low incidence of treatment-related toxicity.* Bone Marrow Transplant 1997, 19(12): 1169.

IMMUNOMODULATING AGENTS

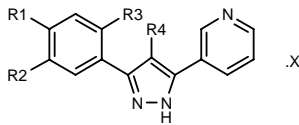
273359

3-[3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl]pyridine hydrochloride



C14 H10 F N3 . HCl; Mol wt: 275.7129

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273363	OMe	H	-(CH2)2-			C ₁₇ H ₁₅ N ₃ O
273365	Cl	H	H	H		C ₁₄ H ₁₀ ClN ₃
273367	OMe	F	H	H		C ₁₅ H ₁₂ FN ₃ O
273368	F	Br	H	H		C ₁₄ H ₉ BrFN ₃

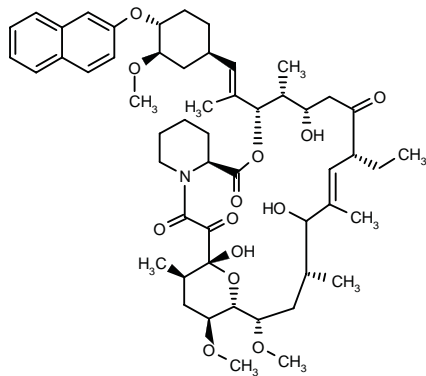
SOURCE – Sumitomo Pharmaceuticals.

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273923

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14,20-trihydroxy-23,25-dimethoxy-12-[2-[3-methoxy-4-(2-naphthalenyloxy)cyclohexyl]-1(*E*)-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone



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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

BUSULFAN

New formulation

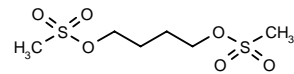
Rec INN; JAN; USAN

231560

1,4-Butanediol dimethanesulfonate

1,4-Bis(methanesulfonyloxy)butane

Busulphan (BAN)
NSC-750



C6 H14 O6 S2; Mol wt: 246.3026

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SOURCE – Orphan Medical.

REFERENCES

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22. *Orphan Medical announces results of Busulfex clinical trials.* DailyDrugNews.com (Daily Essentials) 1998, April 7.

23. *Orphan Medical files NDS for Busulfex Injection in Canada.* DailyDrugNews.com (Daily Essentials) 1998, Dec 17.

24. *Orphan Medical launches improved form of busulfan in U.S.* DailyDrugNews.com (Daily Essentials) 1999, Feb 24.

25. *Orphan Medical's Busulfex Injection approved in U.S.* DailyDrugNews.com (Daily Essentials) 1999, Feb 8.

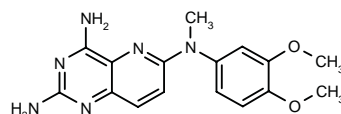
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ANTIMETABOLITES

270355

6-[*N*-(3,4-Dimethoxyphenyl)-*N*-methylamino]pyrido[3,2-*d*]pyrimidine-2,4-diamine



C16 H18 N6 O2; Mol wt: 326.3582

M.p. 207-9 °C.

ACTION – Antineoplastic agent, an analogue of piritrexim that inhibits dehydrofolate reductase (DHFR). Compound exhibited subnanomolar activity against recombinant DHFR from *Pneumocystis carinii* (pcDHFR; IC₅₀ = 2.3 nM), native DHFR from *Toxoplasma gondii* (tgDHFR; IC₅₀ = 0.88 nM) and rat liver DHFR (rlDHFR; IC₅₀ = 0.4 nM), and was at least 3-20-fold more potent than piritrexim (IC₅₀ = 31, 17 and 1.5 nM, respectively). Compound inhibited the growth of a variety of tumor cells such as leukemia, non-small cell lung, colon, CNS, ovarian, renal, prostate and breast cancer, and melanoma cells, with GI₅₀ values < 0.01 μM.

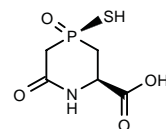
SOURCES – Duquesne University, Pittsburgh, PA (US); Indiana University, Indianapolis, IN (US).

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270359

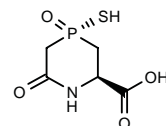
(+)-*cis*-6-Oxo-4-sulfanyl-1,4-azaphosphorinane-2-carboxylic acid *P*-oxide



C5 H8 N O4 P S; Mol wt: 209.1612

M.p. 173-6 °C.

ACTION – Potent inhibitor of mammalian dihydroorotase (K_i = 2.9 ± 0.6 μM) with potential therapeutic application for the treatment of cancer and malaria. Another phosphinothioic acid with similar activity is:



270360: C5 H8 N O4 P S

SOURCE – University of Sydney, Sydney (AU).

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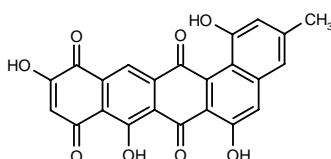
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ANTIBIOTICS AND ALKALOIDS

BE-45985X

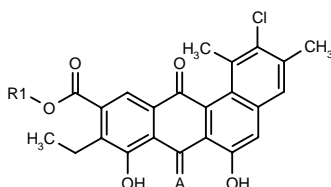
273387

1,6,8,11-Tetrahydroxy-3-methylbenzo[*a*]naphthacene-7,9,12,14-tetraone



C23 H12 O8; Mol wt: 416.3398

ACTION – Antineoplastic agent isolated from the microorganism *Streptomyces* sp. A45985 (FERM P-14707), with *in vitro* cytotoxic activity against murine leukemia P388 (IC₅₀ = 1.6 µg/ml), murine colon cancer 26 (IC₅₀ = 1.2 µg/ml), human colon cancer DLD-1 (IC₅₀ = 1.2 µg/ml), human lung cancer PC-13 (IC₅₀ = 1.4 µg/ml) and human gastric cancer MKN-45 cells (IC₅₀ = 1.9 µg/ml). Other compounds isolated from this microorganism include the following:



Compound	R1	A	Formula
BE-45985A1 [273388]	Me	O	C ₂₄ H ₁₉ ClO ₆
BE-45985A2 [273389]	H	O	C ₂₃ H ₁₇ ClO ₆
BE-45985A3 [273390]	Me	NH	C ₂₄ H ₂₀ ClNO ₅
BE-45985A4 [273391]	H	NH	C ₂₃ H ₁₈ ClNO ₅

SOURCE – Banyu.

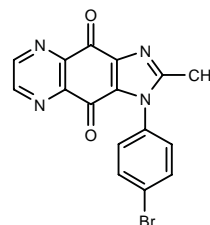
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DNA-INTERCALATING DRUGS

270496

1-(4-Bromophenyl)-2-methyl-4,9-dihydro-1*H*-imidazo[4,5-*g*]quinoxaline-4,9-dione



C16 H9 Br N4 O2; Mol wt: 369.1771

M.p. 279-81 °C.

ACTION – Antineoplastic agent, a DNA-intercalating agent with potent and selective cytotoxic activity against human gastric adenocarcinoma MKN-45 cells (IC₅₀ = 1.30 µM), showing greater potency than either doxorubicin or cisplatin (IC₅₀ = 3.13 and 86.5 µM, respectively); it was, however, significantly less active than reference compounds against human lung adenocarcinoma PC14 cells (IC₅₀ = 45.50, 0.29 and 3.87 µM, respectively) and human colon carcinoma 205 cells.

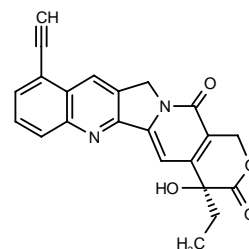
SOURCES – Ewha Womans University, Seoul (KR); Korea Institute of Science and Technology, Seoul (KR).

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272738

4(*S*)-Ethyl-10-ethynyl-4-hydroxy-1*H*-pyrano[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione



C22 H16 N2 O4; Mol wt: 372.3784

ACTION – Antineoplastic agent reported to be active against leukemia and solid tumor cell lines such as colon and rectal tumors. A compound within a series of specifically claimed alkynyl-substituted camptothecin derivatives.

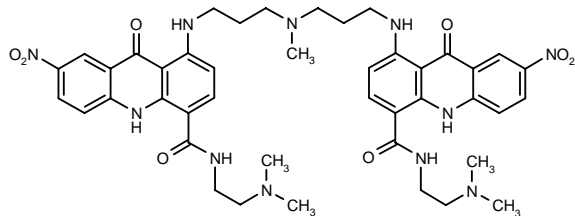
SOURCE – Pharmacia & Upjohn.

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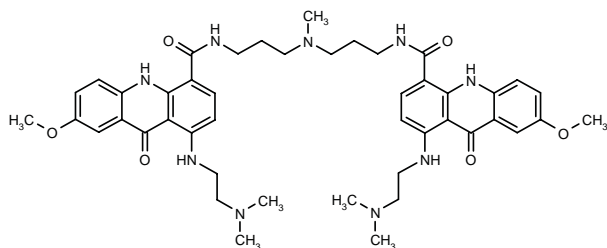
273293

1,1'-(Methylimino)bis(propane-1,3-diyl)bis(imino)bis[N-[2-(dimethylamino)ethyl]-7-nitro-9-oxo-9,10-dihydroacridine-4-carboxamide]

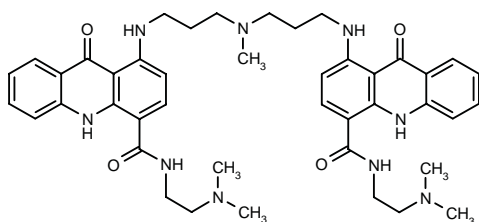


C43 H51 N11 O8; Mol wt: 849.9449

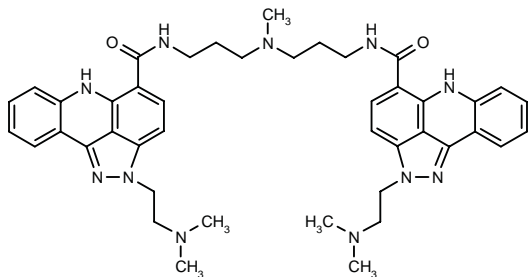
ACTION – Antineoplastic agent for the treatment of solid tumors responding to DNA-intercalating agents, particularly colon cancer, with more potent cytotoxicity against human colon adenocarcinoma HT-29 cells than mitoxantrone ($IC_{50} < 0.0001 \mu\text{g/ml}$ vs. $0.005 \mu\text{g/ml}$ for mitoxantrone). A representative compound from a series of bis-acridinecarboxamides, wherein the following are also included:



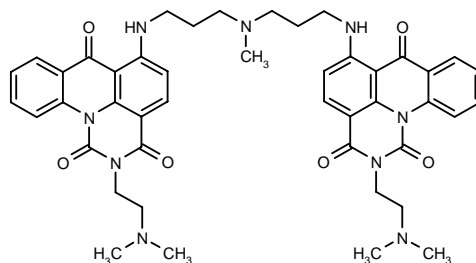
273294: C45 H57 N9 O6



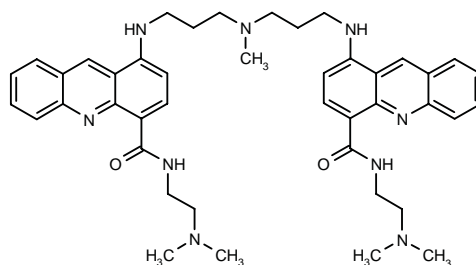
273295: C43 H53 N9 O4



273296: C43 H51 N11 O2



273297: C45 H49 N9 O6



273298: C43 H53 N9 O2

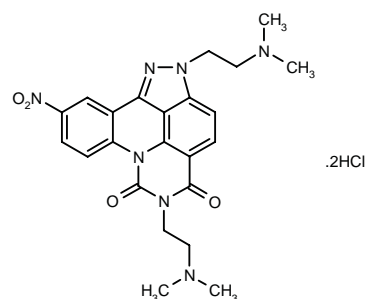
SOURCE – Università degli Studi di Camerino, Camerino (IT).

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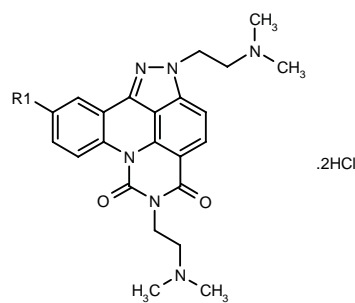
273535

2,6-Bis[2-(dimethylamino)ethyl]-11-nitropyrazolo-[3,4,5-*mn*]pyrimido[5,6,1-*de*]acridine-5,7(2*H*,6*H*)-dione dihydrochloride



C23 H25 N7 O4 . 2HCl; Mol wt: 536.4173

ACTION – Antineoplastic agent particularly suitable for the treatment of colon tumors in view of its remarkable cytotoxicity against human colon adenocarcinoma HT29 cells ($IC_{50} = 0.0004 \mu\text{g/ml}$ vs. $IC_{50} = 0.005 \mu\text{g/ml}$ for mitoxantrone). It is expected to be useful against tumors responding to DNA-intercalating agents. A representative compound from a series of pyrazolo-acridines and pyrazolo-pyrimidoacridines, wherein the following are also included:



Compound	R1	Formula
273538	H	C ₂₃ H ₂₆ N ₆ O ₂ ·2HCl
273539	OMe	C ₂₄ H ₂₆ N ₆ O ₃ ·2HCl
273540	NH2	C ₂₃ H ₂₇ N ₇ O ₂ ·2HCl

SOURCE – Università degli Studi di Camerino, Camerino (IT).

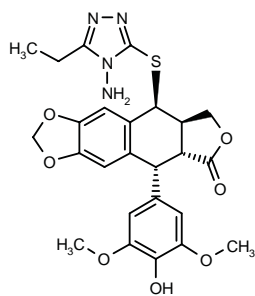
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273557

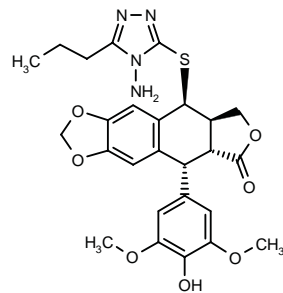
[5*R*-(5α,5aβ,8α,9β)]-9-(4-Amino-5-ethyl-4*H*-1,2,4-triazol-3-ylsulfanyl)-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5*aH*)-one

4-(4-Amino-5-ethyl-4*H*-1,2,4-triazol-3-ylsulfanyl)-4-deoxy-4'-*O*-demethylepipodophyllotoxin



C25 H26 N4 O7 S; Mol wt: 526.5674

ACTION – Antineoplastic agent, a podophyllotoxin analogue with high activity against human erythroleukemia K562 cells. Another compound from this series is:



273558: C26 H28 N4 O7 S

SOURCES – Beijing Medical University, Beijing (CN); Lanzhou University, Lanzhou (CN).

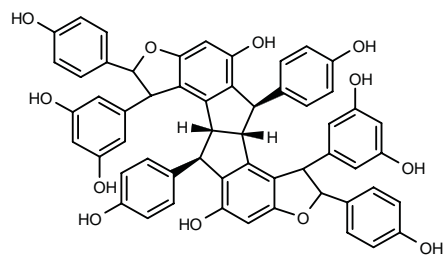
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NEPARENSINOL B

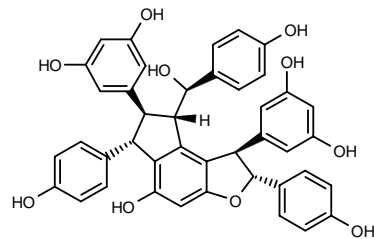
273120

(6*R*,6*aR*,12*R*,12*aR*)-1,7-Bis(3,5-dihydroxyphenyl)-2,6,8,12-tetrakis(4-hydroxyphenyl)-1,2,6,6*a*,7,8,12,12*a*-octahydrofuro[2'',3'':6',7']indeno[1',2':2,3]indeno[5,4-*b*]-furan-5,11-diol

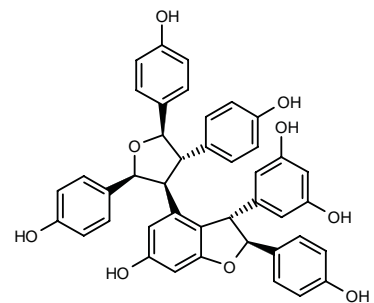


C56 H42 O12; Mol wt: 906.9358

ACTION – Antineoplastic agent isolated from the plant *Kobresia neparensis* that acts by inhibiting topoisomerase II. Other compounds isolated from this source are:



Neparensinol A [273121]: C42 H34 O10



Neparensinol C [273122]: C42 H34 O9

SOURCE – Meiji Milk Products.

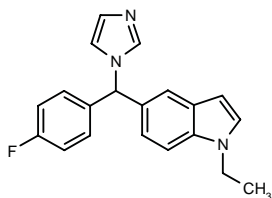
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HORMONAL AGENTS

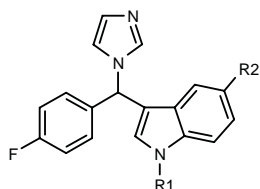
272671

1-Ethyl-5-[(4-fluorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-indole



C₂₀ H₁₈ F N₃; Mol wt: 319.3812

ACTION – Potent and selective, nonsteroidal aromatase inhibitor (IC₅₀ = 0.041 μM) with only moderate effects against androgen biosynthesis, potentially useful for the treatment of estrogen-dependent disorders such as advanced breast cancer in postmenopausal patients.



Compound	R1	R2	Formula
272672	Et	H	C ₂₀ H ₁₈ FN ₃
272673	Me	Br	C ₁₉ H ₁₅ BrFN ₃

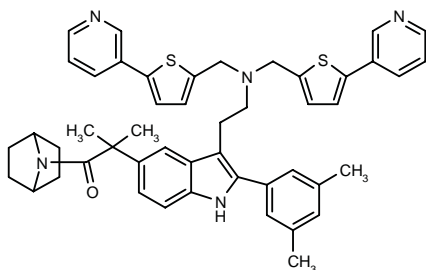
SOURCE – Universität des Saarlandes, Saarbrücken (DE).

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273334

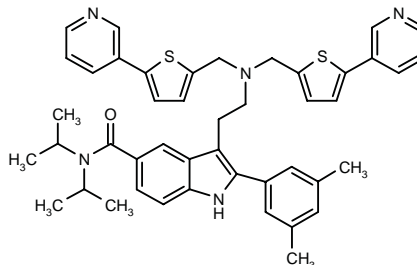
1-(7-Azabicyclo[2.2.1]hept-7-yl)-2-[3-[2-[*N,N*-bis[5-(3-pyridinyl)-2-thienylmethyl]amino]ethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methyl-1-propanone



C₄₈ H₄₉ N₅ O S₂; Mol wt: 776.0811

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist claimed for the treatment of a variety of sex hormone-related conditions including prostate, uterine and breast cancer, endometriosis, polycystic ovarian

disease, benign prostatic hypertrophy, premenstrual syndrome, hirsutism and short stature or growth hormone deficiency, as well as for preventing pregnancy. Additionally claimed for the treatment of lupus erythematosus, irritable bowel syndrome and sleep disorders. Another specifically claimed compound from this series of indole derivatives is:



273335: C₄₅ H₄₇ N₅ O S₂

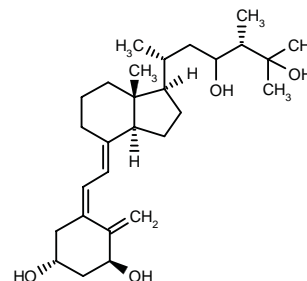
SOURCE – Merck & Co.

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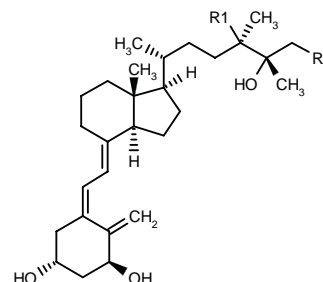
273680

1α,23,25-Trihydroxyvitamin D₄



C₂₈ H₄₆ O₄; Mol wt: 446.6674

ACTION – Vitamin D analogue for the treatment of hyper-proliferative diseases, osteoporosis and immunological disorders with higher affinity for the vitamin D₃ receptor than 1,25-dihydroxyvitamin D₃ and reported to possess little calcemic activity. In addition, it exhibited comparable potency to 1,25-dihydroxyvitamin D₃ in inducing differentiation of HL-60 cells at 0.1 and 0.01 μM. Other compounds from this series of vitamin D analogues include the following:



Compound	R1	R2	Formula
273681	H	OH	C ₂₈ H ₄₆ O ₄
273682	OH	H	C ₂₈ H ₄₆ O ₄

SOURCE – Nisshin Flour Milling.

REFERENCES

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P-X-1544

273683

Conjugate of the GnRH analogue MI-1544 and the copolymer poly(N-vinylpyrrolidone-co-maleic acid) (P) through a Gly-Phe-Leu-Gly (X) spacer

ACTION – Antineoplastic agent, a gonadotropin-releasing hormone (GnRH) antagonist*-copolymer conjugate that reduces the cloning efficiency and inhibits the proliferation of a range of human cancer cell lines with membrane receptors for GnRH such as breast, prostate and endometrial cancer cell lines. Compound inhibited cdc25 phosphatase and caused accumulation of cells in the G2/M phase of the cell cycle after 24 h and in the G1 and G2 phases after 48 h. In mice bearing human breast cancer MCF-7, compound given at a daily dose of 50 µg for 6 weeks induced a significant reduction in tumor mass (65%) and weight (49%); it was also effective against mouse mammary carcinoma MXT in normal mice and human breast cancer MDA-MB-231 xenografts in immunosuppressed mice. Another such conjugate is:

Conjugate of the GnRH analogue MI-1892 and the copolymer poly(N-vinylpyrrolidone-co-maleic acid) (P) through a Gly-Phe-Leu-Gly (X) spacer

P-X-1892 [273684]

SOURCES – Central Research Institute for Chemistry, Budapest (HU); National Institute of Oncology, Budapest (HU); Semmelweis University Medical School, Budapest (HU).

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*See **MI-1544** Drug Data Report 1994, 016(09): 0868.

CANCER IMMUNOTHERAPY

DENILEUKIN DIFTITOX

Prop INN

204626

Recombinant fusion protein in which the receptor-binding domain of native diphtheria toxin (DT) has been replaced with the polypeptide hormone IL-2. This fusion toxin consists of amino acid residues 2-133 of human IL-2 joined in correct translational reading frame to Ala389 of DT. DAB₃₈₉ IL-2 binds to the high-affinity form of the IL-2 receptor and is internalized by receptor-mediated endocytosis

N-L-Methionyl-387-L-histidine-388-L-alanine-1-388-toxin (Corynebacterium diphtheriae strain C7) (388→2')-protein with 2-133-interleukin 2 (human clone pTIL2-21a)

DAB₃₈₉ IL-2+
LY-335348

ACTION – Recombinant DNA-derived cytotoxic fusion protein designed to direct the cytotoxic action of diphtheria toxin to cells expressing the high-affinity IL-2 receptor on their surface such as activated T-lymphocytes, activated B-lymphocytes, activated macrophages and certain malignant cells, inhibiting cellular protein synthesis and resulting in cell death.

INDICATION – Treatment of persistent or recurrent cutaneous T-cell lymphoma (CTCL) in patients whose malignant cells express the CD25 component of the IL-2 receptor.

PRESENTATION – Single-use vials (2 ml), containing 300 µg recombinant denileukin diftotox.

PROPRIETARY NAME – Ontak (US).

SOURCES – Ligand; manufactured by Seragen.

RECENT REFERENCES

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2. Duvic, M. et al. *DAB(389)IL2 diphtheria fusion toxin reduces clinical responses in tumor stage cutaneous T cell lymphoma.* Am J Hematol 1998, 58(1): 87.
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4. Foss, F.M. et al. *Immunohistochemical detection of the p55 component of the high-affinity interleukin-2 receptor alone is sufficient to predict for response to DAB389IL2 (ONTAK).* Proc Amer Soc Clin Oncol 1999, 18 Abst 48.
5. Hu, H.Y. et al. *The effects of helix breaking mutations in the diphtheria toxin transmembrane domain helix layers of the fusion toxin DAB(389)IL-2.* Protein Eng 1998, 11(9): 811.
6. *CBER requests additional information for Ontak BLA.* DailyDrugNews.com (Daily Essentials) 1998, June 19.
7. *FDA advisory committee recommends approval of Ontak for CTCL.* DailyDrugNews.com (Daily Essentials) 1998, June 3.
8. *Ligand and Ferrer enter marketing agreement for five Ligand products.* DailyDrugNews.com (Daily Essentials) 1999, April 7.
9. *Ligand confirms that ECOG has initiated multicenter phase II study of Ontak for NHL.* DailyDrugNews.com (Daily Essentials) 1999, May 13.

10. *Ligand receives FDA approval for Ontak as CTCL treatment.* DailyDrugNews.com (Daily Essentials) 1999, Feb 8.

11. *Ligand to merge with Seragen and acquire Marathon; acquires fusion toxin rights from Lilly.* DailyDrugNews.com (Daily Essentials) 1998, May 12.

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13. *Ontak available this month in U.S.* DailyDrugNews.com (Daily Essentials) 1999, Feb 16.

14. *Seragen fusion toxin will get priority review.* DailyDrugNews.com (Daily Essentials) 1998, Feb 5.

15. *Seragen reports preliminary results of pivotal CTCL study.* DailyDrugNews.com (Daily Essentials) 1997, Dec 17.

16. *Seragen submits BLA for CTCL biological product.* DailyDrugNews.com (Daily Essentials) 1997, Dec 9.

*DAB₃₈₉IL-2 Drug Data Report 1994, 016(04): 0313.

DT₃₈₈-GM-CSF

270607

Recombinant fusion toxin consisting of the first 388 amino acids of diphtheria toxin (catalytic and translocation subunits) linked at its carboxy terminus to human GM-CSF (replacing the binding domain)

ACTION – Antineoplastic agent, a recombinant fusion toxin comprising the catalytic and translocation subunits of diphtheria toxin linked to GM-CSF (granulocyte-macrophage colony-stimulating factor) with potential in the treatment of acute myeloid leukemia (AML), especially as combination therapy for refractory AML, as indicated by results from *in vitro* and *in vivo* studies.

SOURCES – National Institutes of Health, Bethesda, MD (US); Medical University of South Carolina, Charleston, SC (US).

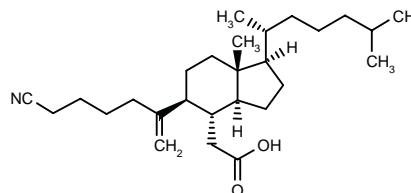
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- Frankel, A.E. et al. *Cell-specific modulation of drug resistance in acute myeloid leukemic blasts by diphtheria fusion toxin, DT388-GMCSF.* Bioconjugate Chem 1998, 9(4): 490.
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- Hall, P.D. et al. *DT388-GM-CSF, a fusion toxin targeting the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor, improves survival of SCID mice bearing human acute myeloid leukemia (AML) blasts over ARA-C.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2535.
- Hall, P.D. et al. *Toxicology and pharmacokinetics of DT388-GM-CSF, a fusion toxin consisting of a truncated diphtheria toxin (DT388) linked to human granulocyte-macrophage colony-stimulating factor (GM-CSF) in C57BL/6 mice.* Toxicol Appl Pharmacol 1998, 150(1): 91.
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- Kreitman, R.J. and Pastan, I. *Recombinant toxins containing human granulocyte-macrophage colony-stimulating factor and either Pseudomonas exotoxin or diphtheria toxin kill gastrointestinal cancer and leukemia cells.* Blood 1997, 90(1): 252.
- Rozemuller, H. et al. *GM-CSF receptor targeted treatment of primary AML in SCID mice using diphtheria toxin fused to huGM-CSF.* Leukemia 1998, 12(12): 1962.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

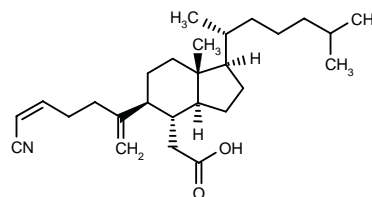
270493

[1*R*-(1 α ,3 α ,4 β ,5 α ,7 α)]-2-[5-(5-Cyano-1-methylene-pentyl)-1-[1(*R*),5-dimethylhexyl]-7 α -methylperhydroinden-4-yl]acetic acid

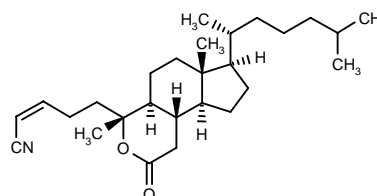


C27 H45 N O2; Mol wt: 415.6575

ACTION – Inhibitor of CDC25A phosphatase with the ability to reversibly inhibit dephosphorylation of fluorescein diphosphate by the enzyme with an IC₅₀ of 2.2 μ M, being more potent than the marine natural product dysidiolide. Potentially useful in cancer therapy. Other related compounds are:



270491: C27 H43 N O2



270492: C27 H43 N O2

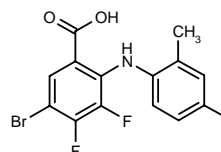
SOURCES – University of Arizona, Tucson, AZ (US); Georgia Institute of Technology, Atlanta, GA (US); Mayo Clinic, Rochester, MN (US).

REFERENCES

- Peng, H. et al. *Novel CDC25A phosphatase inhibitors from pyrolysis of 3- α -azido-B-homo-6-oxa-4-cholesten-7-one on silica gel.* J Med Chem 1998, 41(24): 4677.

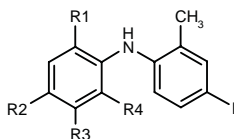
272355

5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid



C14 H9 Br F2 I N O2; Mol wt: 468.0301

ACTION – Agent for the treatment of cancer and other proliferative diseases, a highly specific and potent inhibitor of MEK kinase activity ($IC_{50} = 0.005 \mu M$). Within this series of specifically claimed 2-(4-bromo or 4-iodo phenylamino)-benzoic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
272356	CO ₂ H	F	F	F	C ₁₄ H ₉ F ₃ INO ₂
272357	CO ₂ H	H	F	F	C ₁₄ H ₁₀ F ₂ INO ₂
272358	CO ₂ H	H	H	H	C ₁₄ H ₁₂ INO ₂
272359	CO ₂ H	H	NO ₂	H	C ₁₄ H ₁₁ IN ₂ O ₄
272360	CH ₂ OH	H	F	H	C ₁₄ H ₁₃ FINO
272361	CONHCH ₂ CH ₂ OH	Br	F	F	C ₁₆ H ₁₄ BrF ₂ IN ₂ O ₂

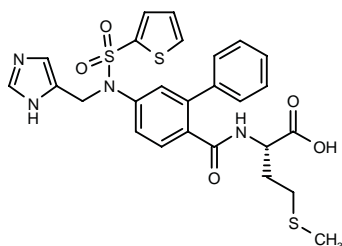
SOURCE – Warner-Lambert.

REFERENCES

1. Barrett, S.D. et al. (Warner-Lambert Co.) 2-(4-Bromo or iodo phenylamino)benzoic acid derivs. and their use as MEK inhibitors. WO 9901421.

273172

N-[5-[*N*-(1*H*-Imidazol-5-ylmethyl)-2-thienylsulfonamido]-biphenyl-2-ylcarbonyl]-L-methionine



C26 H26 N4 O5 S3; Mol wt: 570.7124

ACTION – Agent for the treatment of cancer, restenosis and atherosclerosis, an inhibitor of protein prenylation, in particular of protein farnesyltransferase ($IC_{50} = 29 \text{ nM}$) and protein geranylgeranyltransferase. A representative compound within a series of sulfonamide derivatives.

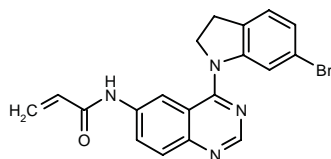
SOURCE – Pierre Fabre.

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1. Gotteland, J.-P. et al. (Pierre Fabre Médicament) Novel sulphonamide derived from substd. anilines useful as medicines. WO 9906376.

273178

N-[4-(6-Bromo-2,3-dihydro-1*H*-indol-1-yl)-6-quinazolinyl]-2-propenamide



C19 H15 Br N4 O; Mol wt: 395.2585

ACTION – An irreversible inhibitor of human epidermal growth factor (EGF) receptor tyrosine kinase ($IC_{50} = 0.4 \text{ nM}$) potentially useful for the treatment of cancer, restenosis, atherosclerosis, endometriosis and psoriasis. A representative compound within a series of specifically claimed bicyclic derivatives.

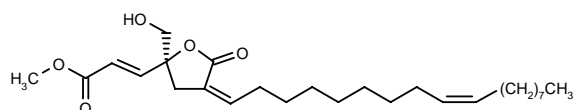
SOURCE – Warner-Lambert.

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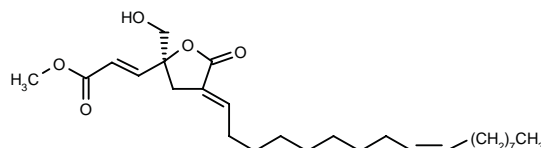
273191

(*Z*)-3-[2(*S*)-(Hydroxymethyl)-4-[9(*Z*)-octadecenylidene]-5-oxotetrahydrofuran-2-yl]-2(*E*)-propenoic acid methyl ester



C27 H44 O5; Mol wt: 448.6396

ACTION – Agent with high affinity for protein kinase C (PKC) ($K_i = 11 \text{ nM}$) that acts as an agonist or partial antagonist in intact cells, potentially useful for the treatment of leukemia and melanoma, as well as inflammatory disorders such as psoriasis and dermatitis. Another specifically claimed conformationally constrained (metabolically stable) diacylglycerol analogue is:



273192: C27 H44 O5

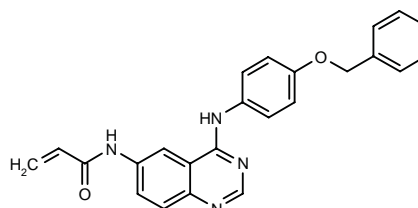
SOURCE – Department of Health & Human Services (US).

REFERENCES

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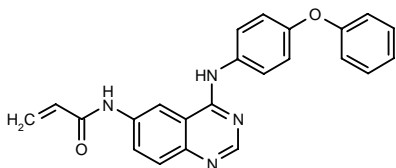
273466

N-[4-[4-(Benzyloxy)phenylamino]-6-quinazolinyl]-2-propenamide



C24 H20 N4 O2; Mol wt: 396.4480

ACTION – An irreversible inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase (IC_{50} = 3.6 nM against enzyme isolated from human epidermoid carcinoma A431 cells) for the treatment of cancer, restenosis, atherosclerosis, endometriosis and psoriasis. Another representative compound is:



273468: C₂₃ H₁₈ N₄ O₂

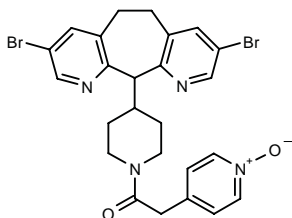
SOURCE – Warner-Lambert.

REFERENCES

1. Bridges, A.J. (Warner-Lambert Co.) *Irreversible inhibitors of tyrosine kinases*. WO 9906378.

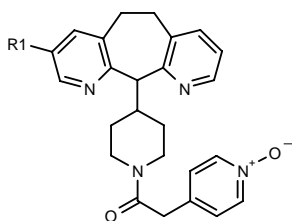
273922

1-[4-(3,8-Dibromo-6,11-dihydro-5H-pyrido[3',2':5,6]-cyclohepta[1,2-b]pyridin-11-yl)-1-piperidiny]-2-(1-oxidopyridin-4-yl)ethanone



C₂₅ H₂₄ Br₂ N₄ O₂; Mol wt: 572.2986

ACTION – Antineoplastic agent, a selective inhibitor of protein farnesyltransferase (IC_{50} = 0.028 μ M) proven to inhibit Ras processing in COS cells with an IC_{50} of 0.125 μ M. Compound is also reported to possess antihistaminic activity and therefore to be useful as an antiallergic agent. Other specifically claimed compounds within this series of bispyridocycloheptanes include the following:



Compound	R1	Formula
273925	Br	C ₂₅ H ₂₅ BrN ₄ O ₂
273928	Me	C ₂₆ H ₂₈ N ₄ O ₂

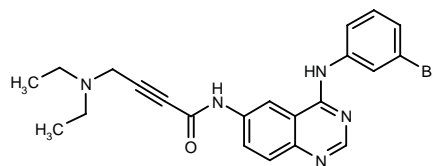
SOURCE – Schering-Plough.

REFERENCES

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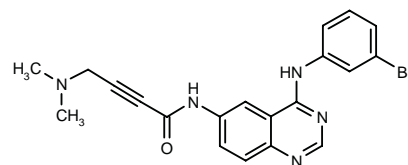
273999

N-[4-(3-Bromophenylamino)-6-quinazoliny]-4-(diethylamino)-2-butyamide



C₂₂ H₂₂ Br N₅ O; Mol wt: 452.3538

ACTION – Antineoplastic agent, an inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase (IC_{50} = 0.014 μ M using recombinant enzyme). *In vitro*, compound was shown to inhibit the growth of human breast cancer MB435, human ovarian cancer A2780S and A2780DDP, human breast cancer MCF-7, human colon cancer SW620, human melanoma LOX, human epidermoid carcinoma A431 and human breast cancer SKBR3 cells with respective IC_{50} values of 0.05, 0.04, 0.04, 0.74, 0.07, 0.1, 0.06 and 0.004 μ M. *In vivo*, compound inhibited the growth of A431 tumors implanted s.c. in mice, giving a T/C x 100 value of 52% at day 28 after tumor implantation when administered at a dose of 40 mg/kg/day p.o. x 10 days. Compound is also reported to be useful for the treatment of certain kidney diseases such as polycystic kidney disease. Another exemplified compound within this series of substituted quinazoline derivatives is:



274002: C₂₀ H₁₈ Br N₅ O

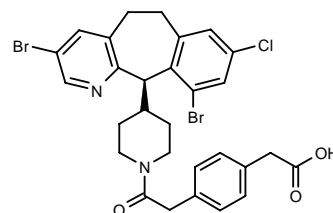
SOURCE – American Home Products.

REFERENCES

1. Wissner, A. et al. (American Cyanamid Co.) *Subst. quinazoline derivs. and their use as tyrosine kinase inhibitors*. WO 9909016.

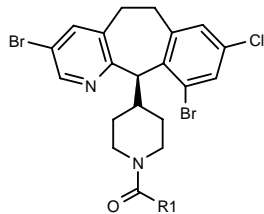
274292

2-[4-[2-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(R)-yl]piperidin-1-yl]-2-oxoethyl]phenyl]acetic acid



C₂₉ H₂₇ Br₂ Cl N₂ O₃; Mol wt: 646.8043

ACTION – Antineoplastic agent, a selective inhibitor of protein farnesyltransferase reported to inhibit Ras processing in COS cells with an IC₅₀ value in the range 0.010-0.50 μM. Other compounds within this series of benzo[5,6]cyclohepta[1,2-*b*]pyridine derivatives include the following:



Compound	R1	Formula
274294	3-(CO2HCH2)-PhCH2	C ₂₉ H ₂₇ Br ₂ ClN ₂ O ₃
274296	4-(EtOCO)-cyclohexyl-CH2	C ₃₀ H ₃₅ Br ₂ ClN ₂ O ₃
274298	3-(MeOCOCH2NHCOCH2)-PhCH2	C ₃₂ H ₃₂ Br ₂ ClN ₃ O ₄
274299	4-(MeOCOCH2NHCOCH2)-PhCH2	C ₃₂ H ₃₂ Br ₂ ClN ₃ O ₄
274300	4-(MeONHCOCH2)-PhCH2	C ₃₀ H ₃₀ Br ₂ ClN ₃ O ₃
274301	4-(NH2COCH2)-cyclohexyl-CH2	C ₂₉ H ₃₄ Br ₂ ClN ₃ O ₂
274302	4-(NH2CO)-cyclohexyl-CH2	C ₂₈ H ₃₂ Br ₂ ClN ₃ O ₂
274303	(1S,2S)-2-(NH2CO)-cyclopropyl	C ₂₄ H ₂₄ Br ₂ ClN ₃ O ₂
274304	4-(MeOCOCH2)-PhCH2	C ₃₀ H ₂₈ Br ₂ ClN ₂ O ₃
274305	cis-4-(CO2HCH2)-cyclohexyl-CH2	C ₂₉ H ₃₃ Br ₂ ClN ₂ O ₃
274306	trans-4-(CO2HCH2)-cyclohexyl-CH2	C ₂₉ H ₃₃ Br ₂ ClN ₂ O ₃

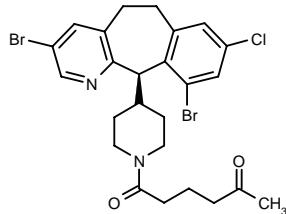
SOURCE – Schering-Plough.

REFERENCES

1. Guzi, T.J. and Rane, D.F. (Schering Corp.) *Benzo(5,6)cyclohepta(1,2-b)pyridine derivs. as farnesyl protein transferase inhibitors.* WO 9857945.

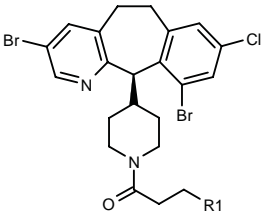
274307

1-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]hexane-1,5-dione



C25 H27 Br2 Cl N2 O2; Mol wt: 582.7613

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase (IC₅₀ = 7.6 nM) proven to inhibit Ras processing in COS cells (IC₅₀ = 10 nM). Other exemplified compounds within this series of tricyclic keto amide derivatives include the following:



Compound	R1	Formula
274308	Ac	C ₂₄ H ₂₅ Br ₂ ClN ₂ O ₂
274309	COCH2Ac	C ₂₆ H ₂₇ Br ₂ ClN ₂ O ₃
274310	C(Me)=NOH	C ₂₄ H ₂₆ Br ₂ ClN ₃ O ₂
274311	C(Ph)=NOH	C ₂₉ H ₂₈ Br ₂ ClN ₃ O ₂
274312	C(Me)=NNHCONH2	C ₂₅ H ₂₈ Br ₂ ClN ₅ O ₂
274313	C(Me)=NNHCOCONH2	C ₂₆ H ₂₈ Br ₂ ClN ₅ O ₃

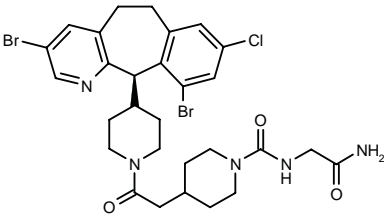
SOURCE – Schering-Plough.

REFERENCES

1. Doll, R.J. et al. (Schering Corp.) *Tricyclic keto amide derivs. useful as farnesyl protein transferase inhibitors.* WO 9857947.

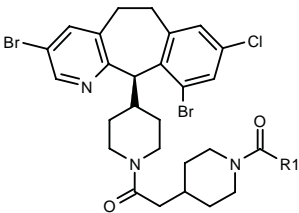
274314

*N*²-[4-[2-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-2-oxoethyl]piperidin-1-ylcarbonyl]glycinamide



C29 H34 Br2 Cl N5 O3; Mol wt: 695.8806

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase (IC₅₀ = 0.9 nM) proven to inhibit Ras processing in COS cells (IC₅₀ = 25 nM). Other compounds within this series of *N*-substituted urea derivatives include the following:



Compound	R1	Formula
274315	NHMe	C ₂₈ H ₃₃ Br ₂ ClN ₄ O ₂
274316	NHCH2CO2Me	C ₃₀ H ₃₅ Br ₂ ClN ₄ O ₄
274317	1-(EtOCO)-4-Pip	C ₃₅ H ₄₃ Br ₂ ClN ₄ O ₄
274318	N(CH2CH2OH)2	C ₃₁ H ₃₉ Br ₂ ClN ₄ O ₄
274319	NHCH2CH2OH	C ₂₉ H ₃₅ Br ₂ ClN ₄ O ₃
274320	NHCH2CO2H	C ₂₉ H ₃₃ Br ₂ ClN ₄ O ₄

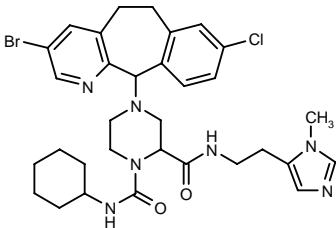
SOURCE – Schering-Plough.

REFERENCES

1. Remiszewski, S. and Mallams, A.K. (Schering Corp.) *Novel N-substd. urea inhibitors of farnesyl-protein transferase*. WO 9857948.

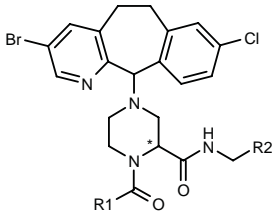
274338

4-(3-Bromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)-1-(*N*-cyclohexyl-carbamoyl)-*N*-[2-(1-methyl-5-imidazolyl)ethyl]piperazine-2-carboxamide



C32 H39 Br Cl N7 O2; Mol wt: 669.0641

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase ($IC_{50} = 7.3 \pm 3$ nM) proven to inhibit Ras processing in COS cells ($IC_{50} = 0.4$ nM). Other compounds within this series of benzo[5,6]-cycloheptapyridine derivatives include the following:



Compound	R1	R2	*Isomer	Formula
274339	Bu	3-Pyr	R	C ₃₀ H ₃₃ BrClN ₅ O ₂
274340	C5H11	3-Pyr		C ₃₁ H ₃₅ BrClN ₅ O ₂
274341	cyclohexyl-NH	3-Pyr	R	C ₃₂ H ₃₆ BrClN ₆ O ₂
274342	cyclohexyl-NH	3-Pyr		C ₃₂ H ₃₆ BrClN ₆ O ₂
274343	cyclopentyl-NH	3-Pyr		C ₃₁ H ₃₄ BrClN ₆ O ₂
274344	CH2CH2-CON(Me)2	3-Pyr		C ₃₁ H ₃₄ BrClN ₆ O ₃
274346	cycloheptyl	3-Pyr		C ₃₃ H ₃₇ BrClN ₅ O ₂
274348	i-BuNH	3-Pyr		C ₃₀ H ₃₄ BrClN ₆ O ₂
274350	cycloheptyl-NH	3-Pyr		C ₃₃ H ₃₈ BrClN ₆ O ₂
274351	cyclohexyl-CH2NH	3-Pyr	R	C ₃₃ H ₃₈ BrClN ₆ O ₂
274353	i-Bu	3-Pyr		C ₃₀ H ₃₃ BrClN ₅ O ₂
274356	cyclohexyl-NH	4-imidazolyl-CH2	R	C ₃₁ H ₃₇ BrClN ₇ O ₂
274358	cyclohexyl-NH	1-imidazolyl-CH2CH2		C ₃₂ H ₃₉ BrClN ₇ O ₂

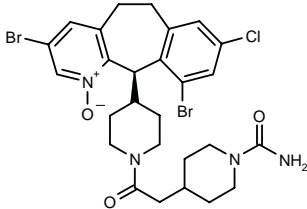
SOURCES – Pharmacopeia; Schering-Plough.

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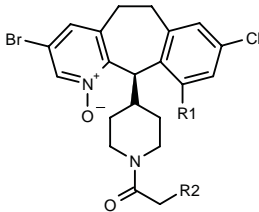
274364

4-[2-[4-[3,10-Dibromo-8-chloro-1-oxido-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide



C27 H31 Br2 Cl N4 O3; Mol wt: 654.8279

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Other compounds within this series of specifically claimed benzo[5,6]cyclohepta[1,2-*b*]pyridine derivatives include the following:



Compound	R1	R2	Formula
274365	H	1-oxido-4-Pyr	C ₂₆ H ₂₅ BrClN ₃ O ₃
274366	Br	1-oxido-4-Pyr	C ₂₆ H ₂₄ Br ₂ ClN ₃ O ₃
274367	H	1-(NH2CO)-4-Pip	C ₂₇ H ₃₂ BrClN ₄ O ₃

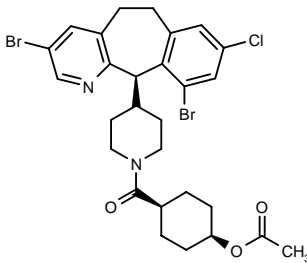
SOURCE – Schering-Plough.

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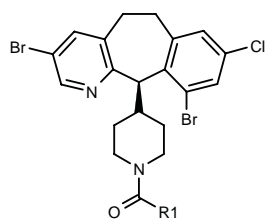
274381

1-(*cis*-4-Acetoxycyclohexyl)-1-[4-[3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]methanone



C28 H31 Br2 Cl N2 O3; Mol wt: 638.8249

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase proven to inhibit Ras processing in COS cells ($IC_{50} = 30$ nM). Other exemplified compounds within this series of benzo-[5,6]cyclohepta[1,2-*b*]pyridine derivatives include the following:



Compound	R1	Formula
274382	4-oxo-cyclohexyl-CH2	C ₂₇ H ₂₅ Br ₂ ClN ₂ O ₂
274383	2-oxo-cyclohexyl-CH2CH2	C ₂₈ H ₃₁ Br ₂ ClN ₂ O ₂
274384	4-(HON=)-cyclohexyl-CH2	C ₂₇ H ₃₀ Br ₂ ClN ₃ O ₂
274385	1,4-dioxo-8-azaspiro-[4.5]dec-8-yl-CH2	C ₂₈ H ₃₂ Br ₂ ClN ₃ O ₃
274389	trans-4-[2-oxo-4(S)-imidazolidinyl-CONH]-cyclohexyl	C ₃₀ H ₃₄ Br ₂ ClN ₅ O ₃
274390	3-(4-oxo-cyclohexyl-CONH)-cyclohexyl	C ₃₃ H ₃₆ Br ₂ ClN ₃ O ₃
274391	trans-4-(NH2CONH)-cyclohexyl-CH2	C ₂₈ H ₃₃ Br ₂ ClN ₄ O ₂
274392	trans-3-OH-cyclohexyl	C ₂₆ H ₂₆ Br ₂ ClN ₂ O ₂
274393	trans-4-(HOCH2CH2NHCOO)-cyclohexyl	C ₂₉ H ₃₄ Br ₂ ClN ₃ O ₄
274395	3-AcO-5-OH-cyclohexyl	C ₂₈ H ₃₁ Br ₂ ClN ₂ O ₄
274396	3,5-(NH2COO)2-cyclohexyl	C ₂₈ H ₃₁ Br ₂ ClN ₄ O ₅

SOURCE – Schering-Plough.

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B43(Anti-CD19)-GENISTEIN

270606

Immunoconjugate constructed by linking the CD19-receptor specific monoclonal antibody B43 to the naturally occurring isoflavone tyrosine kinase inhibitor genistein

ACTION – Antineoplastic immunoconjugate comprising the anti-CD19 antibody B43, which binds with high affinity to the CD19 receptor on Burkitt’s lymphoma cells, and the tyrosine kinase inhibitor genistein. The immunoconjugate triggered rapid apoptotic cell death of RAMOS Burkitt’s lymphoma cells and selectively inhibited the CD19-associated Lck kinase activity, with a decrease in tyrosine phosphorylation of target cell proteins. In mice bearing human B-lineage lymphoma, compound (25 µg/mouse i.v.) prolonged the survival time to over 4 months without clinical evidence of lymphoma. Phase I clinical studies in patients with relapsed or refractory B-lineage acute lymphoblastic leukemia (ALL) demonstrated that the immunoconjugate can be safely administered at doses up to 0.32 mg/kg/day for 10 consecutive days and can potentially induce complete remissions in heavily pretreated patients.

SOURCES – University of Minnesota, Minneapolis, MN (US); Wayne Hughes Institute, St. Paul, MN (US).

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5. Messinger, Y. et al. *In vivo toxicity, pharmacokinetic features and immunogenicity of B43 (ANTI-CD19)-genistein immunoconjugate in mice and non-human primates*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 1467.

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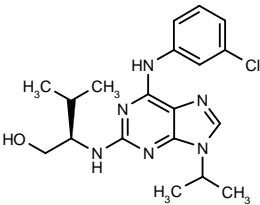
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NG-60

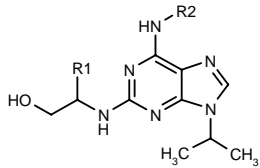
273824

2(R)-[6-(3-Chlorophenylamino)-9-isopropyl-9H-purin-2-ylamino]-3-methyl-1-butanol



C19 H25 Cl N6 O; Mol wt: 388.9005

ACTION – Agent for the treatment of proliferative disorders and neurodegenerative diseases that acts by inhibiting cyclin-dependent kinases CDK1 and CDK2, with IC₅₀ values of 35 and 30 nM, respectively. A representative compound from a series of purine analogues, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
NG-56 [273825]	i-Pr	3-Cl-Ph	racemic	C ₁₉ H ₂₅ ClN ₆ O
NG-35 [273827]	i-Pr	4-MeO-PhCH2	racemic	C ₂₁ H ₃₀ N ₆ O ₂
NG-33 [273829]	Et	4-MeO-PhCH2	R	C ₂₀ H ₂₈ N ₆ O ₂
NG-36 [273832]	i-Bu	4-MeO-PhCH2	R	C ₂₂ H ₃₂ N ₆ O ₂
NG-95 [273834]	i-Pr	3-Cl-4-CO2H-Ph	R	C ₂₀ H ₂₅ ClN ₆ O ₃
NG-96 [273835]	i-Pr	4-Cl-3-CO2H-Ph	R	C ₂₀ H ₂₅ ClN ₆ O ₃
NG-97 [273837]	i-Pr	3-NH2-5-Cl-Ph	R	C ₁₉ H ₂₆ ClN ₇ O
NG-98 [273838]	i-Pr	3-NH2-4-Cl-Ph	R	C ₁₉ H ₂₆ ClN ₇ O
NG-94 [273840]	i-Pr	4-OH-3-CO2H-Ph	R	C ₂₀ H ₂₆ N ₆ O ₄

SOURCE – University of California, Oakland, Oakland, CA (US).

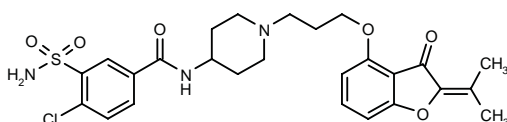
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ANGIOGENESIS INHIBITORS

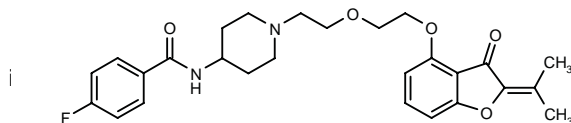
273463

4-Chloro-*N*-[1-[3-[2-isopropylidene-3-oxo-2,3-dihydro-1-benzofuran-4-yloxy]propyl]-4-piperidiny]-3-sulfamoylbenzamide



C26 H30 Cl N3 O6 S; Mol wt: 548.0570

ACTION – Antineoplastic and antimetastatic agent that displays uPA (urokinase-type plasminogen activator)-antagonist activity ($IC_{50} = 0.05 \mu\text{g/ml}$ against binding of human urokinase to its specific receptor uPAR). Other specifically claimed 2-alkylidene hydroxycumarones



273464: C27 H31 F N2 O5

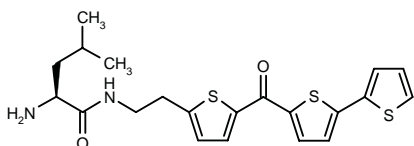
SOURCE – Roche.

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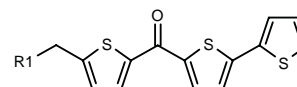
273471

*N*¹-[2-[5-[5-(2-Thienyl)-2-thienylcarbonyl]-2-thienyl]ethyl]-L-leucinamide



C21 H24 N2 O2 S3; Mol wt: 432.6306

ACTION – Antineoplastic, antimetastatic and antiangiogenic agent, an inhibitor of urokinase plasminogen activator (uPA) binding to uPAR ($IC_{50} = 0.002 \text{ mM}$). Other compounds from this series of oligo-thiophenes acting as uPAR antagonists include the following:



Compound	R1	Formula
273472	-CO-L-Trp-OH	C ₂₆ H ₂₀ N ₂ O ₄ S ₃
273473	-CO-L-Phe-OH	C ₂₄ H ₁₉ NO ₄ S ₃
273474	4-F-PhCOCH ₂	C ₂₂ H ₁₅ FO ₂ S ₃
273475	2-thienyl-COCH ₂	C ₂₀ H ₁₄ O ₂ S ₄

SOURCE – Roche.

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MV833

273088

Anti-vascular endothelial growth factor (VEGF) monoclonal antibody

Anti-VEGF MAb

ACTION – Antineoplastic agent, a monoclonal antibody neutralizing human vascular endothelial growth factor (VEGF) with antiangiogenic and antitumor activity against various tumor cell lines secreting VEGF and originating from human solid tumors including colon, lung, breast, pancreas and melanoma tumors implanted in nude mice; MV-833 did not inhibit tumor growth *in vitro*. Compound strongly inhibited *in vivo* tumor growth even after delayed administration, as well as tumor-induced neovascularization in fibrosarcoma HT-1080 cell-implanted nude mice.

SOURCE – Toagosei.

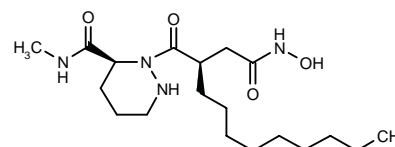
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R-94138

231259

3(*R*)-[3(*S*)-(N-Methylcarbamoyl)hexahydropyridazin-2-ylcarbonyl]dodecanehydroxamic acid



C19 H36 N4 O4; Mol wt: 384.5174

ACTION – Matrix metalloproteinase (MMP) inhibitor, a synthetic derivative of matlystatins with particularly potent activity against gelatinase B (MMP-9; $IC_{50} = 1.2$ nM), as well as against stromelysin (MMP-3) and gelatinase A (MMP-2) *in vitro* ($IC_{50} = 28$ and 38 nM, respectively). In nude mice, compound significantly inhibited peritoneal dissemination of human gastric cancer TMK-1 at i.p. doses of 20-30 mg/kg/day for 5 days. When compound was administered in combination with mitomycin C and cisplatin, its preventive effect in this model was strongly increased.

SOURCE – Sankyo.

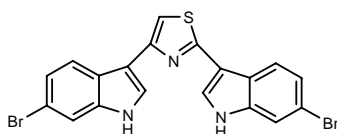
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OTHER ONCOLYTIC DRUGS

273094

2,4-Bis(6-bromo-1*H*-indol-3-yl)thiazole



C₁₉ H₁₁ Br₂ N₃ S; Mol wt: 473.1909

ACTION – Antineoplastic agent, an analogue of the marine bis(indole)alkaloids nortopsentins with *in vitro* cytotoxic activity against a variety of human cancer cell lines ($GI_{50} = 2.94$ - 14.1 μ M).

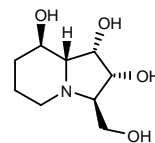
SOURCE – Shanghai Institute of Organic Chemistry, Shanghai (CN).

REFERENCES

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273158

(1*S*,2*R*,3*R*,8*R*,8*aR*)-3-(Hydroxymethyl)octahydroindolizine-1,2,8-triol



C₉ H₁₇ N O₄; Mol wt: 203.2363

ACTION – Antineoplastic agent that acts by inhibiting α -mannosidase ($IC_{50} = 1.2$ μ M), a derivative of swainsonine ($IC_{50} = 0.1$ μ M).

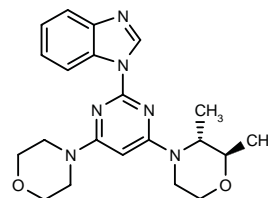
SOURCE – University of Michigan, Ann Arbor, MI (US).

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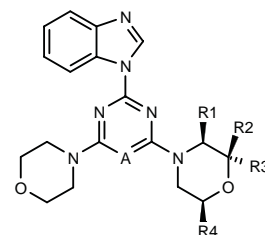
273447

trans-1-[4-(2,3-dimethylmorpholin-4-yl)-6-(4-morpholinyl)-2-pyrimidinyl]-1*H*-benzimidazole



C₂₁ H₂₆ N₆ O₂; Mol wt: 394.4764

ACTION – Antineoplastic agent found to inhibit the growth of human breast cancer MCF-7 cells *in vitro* ($GI_{50} = 2.2$ μ M), as well as tumor growth in mice inoculated with mouse reticuloendothelioma M5070 cells (83.8% inhibition at 100 mg/kg/day, i.p. on days 1-9 post-implantation). $LD_{50} = 400$ - 800 mg/kg p.o. or i.p. in mice. Within this series of heterocyclic compounds, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
273448	H	Me	H	Me	N	C ₂₀ H ₂₅ N ₇ O ₂
273449	Me	Me	H	H	N	C ₂₀ H ₂₅ N ₇ O ₂
273450	Me	H	Me	H	N	C ₂₀ H ₂₅ N ₇ O ₂
273451	H	Me	Me	H	N	C ₂₀ H ₂₅ N ₇ O ₂
273452	H	Me	H	Me	CH	C ₂₁ H ₂₆ N ₆ O ₂
273453	Me	Me	H	H	CH	C ₂₁ H ₂₆ N ₆ O ₂

SOURCE – Zenyaku Kogyo.

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PERILLYL ALCOHOL

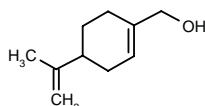
223558

4-Isopropenyl-1-cyclohexenemethanol

NSC-641066

POH

POM



C10 H16 O; Mol wt: 152.2354

ACTION – Antineoplastic agent, a naturally occurring monoterpene with anticarcinogenic and antitumor activity in preclinical models. Apoptosis induced by the agent appears to involve upregulation of the transforming growth factor β (TGF- β) signaling pathway. Currently undergoing phase I clinical trials in patients with advanced malignances. Preliminary results have demonstrated that the compound is well tolerated at up to 1200 mg/m² p.o. q.i.d. and responses have been obtained in metastatic colorectal cancer and metastatic, hormone-refractory prostate cancer.

SOURCES – Endorex; Wisconsin Alumni Research Foundation, Madison, WI (US).

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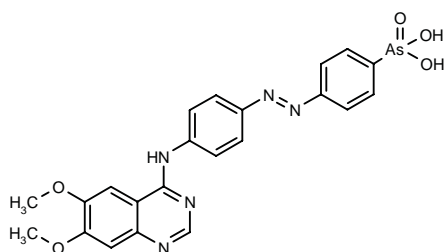
41. *Endorex updates cancer and drug delivery programs.* DailyDrugNews.com (Daily Essentials) 1999, March 3.

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WHI-P273

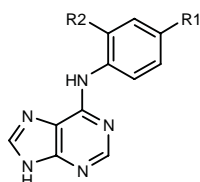
274038

4-[2-[4-(6,7-Dimethoxyquinazolin-4-ylamino)phenyl]-diazenyl]phenylarsonic acid

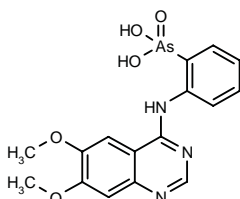


C22 H20 As N5 O5; Mol wt: 509.3520

ACTION – Antineoplastic agent with significant cytotoxic activity against various leukemia cell lines such as NALM-6 and MOLT-3 cells (100% growth inhibition at 10 μ M; IC₅₀ = 7.3 and 12.1 μ M, respectively). Other phenylarsonic acid substituted compounds include the following:



Compound	R1	R2	Formula
WHI-P371 [274040]	4-[AsO(OH)2]-PhN=N	H	C ₁₇ H ₁₄ AsN ₇ O ₃
WHI-P380 [274042]	H	AsO(OH)2	C ₁₁ H ₁₀ AsN ₅ O ₃



WHI-P370 [274039]: C16 H16 As N3 O5

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

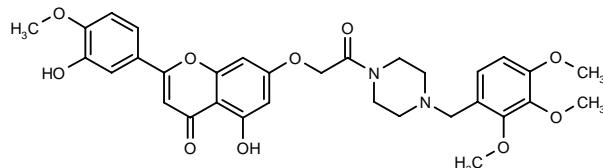
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

273123

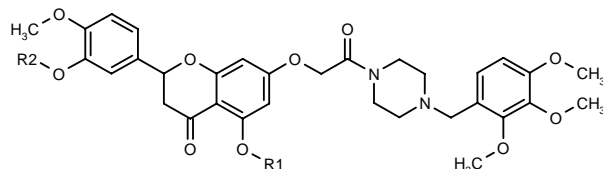
5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[4-(2,3,4-trimethoxybenzyl)piperazin-1-ylcarbonylmethoxy]-4H-benzopyran-4-one



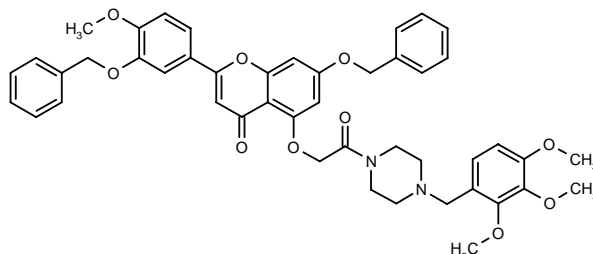
C32 H34 N2 O10; Mol wt: 606.6246

Amorphous.

ACTION – Multidrug resistance (MDR) modulator, a flavonoid derivative with the ability to potentiate the cytotoxicity of doxorubicin (DOX) against drug-resistant human erythroleukemia K562 cells (11- and 78-fold increase of DOX cytotoxicity, respectively, at 1 and 5 μ M). Compound appears to act, at least in part, by inhibiting P-glycoprotein transport, facilitating the penetration of the antitumor drug into the cell. Other related flavonoid compounds are:



Compound	R1=R2	Formula
273126	H	C ₃₂ H ₃₆ N ₂ O ₁₀
273128	t-BuCO	C ₄₂ H ₅₂ N ₂ O ₁₂



273125: C46 H46 N2 O10

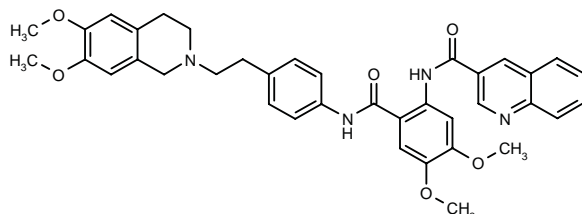
SOURCE – Servier.

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- Ferté, J. et al. *Flavonoid-related modulators of multidrug resistance: Synthesis, pharmacological activity, and structure-activity relationships.* J Med Chem 1999, 42(3): 478.

XR-9576***265879**

N-[2-[*N*-[4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]phenyl]carbamoyl]-4,5-dimethoxyphenyl]quinoline-3-carboxamide



C38 H38 N4 O6; Mol wt: 646.7402

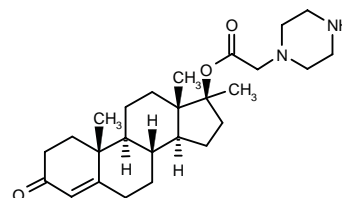
ACTION – Multidrug resistance (MDR) modulator, an anthranilic acid derivative that potentiates the cytotoxic effects of doxorubicin, vincristine, etoposide and paclitaxel against a variety of human and murine P-glycoprotein-expressing MDR cell lines, with IC₅₀ values in the range of 12-40 nM. Compound shows a long duration of action, superior to other MDR modulators such as verapamil and ciclosporin. *In vivo*, compound (5 mg/kg i.v.) significantly enhanced the antitumor activity of doxorubicin in mice with resistant colon carcinoma MC26, and it potentiated the efficacy of etoposide and vincristine in mice with small cell lung carcinoma H69/LX4 xenografts after both oral (6, 12, 245 mg/kg) or i.v. (4, 10 mg/kg) administration. It is in phase II evaluation.

SOURCE – Xenova.**REFERENCES**

1. Ryder, H. et al. (Xenova Group plc) *Anthranilic acid derivs. as multi drug resistance modulators*. WO 9817648.
2. Mistry, P. et al. *In vitro and in vivo evaluation of XR9576, a novel potent modulator of P-glycoprotein (P-gp) mediated multidrug resistance (MDR)*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2079.
3. Mistry, P. et al. *Reversal of P-glycoprotein mediated multidrug resistance in vivo by XR9576*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 568.
4. Roe, M. et al. *Reversal of P-glycoprotein mediated multidrug resistance by novel anthranilamide derivatives*. Bioorg Med Chem Lett 1999, 9(4): 595.
5. Stewart, A.J. et al. *An intravenous phase I study with the novel P-glycoprotein-dependent multidrug resistance modulator, XR9576, demonstrates surrogate marker activity in situ*. Proc Amer Soc Clin Oncol 1999, 18: Abst 704.
6. Stewart, A.J. et al. *XR9576, a potent modulator of P-glycoprotein-mediated multidrug resistance*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 556.
7. *Phase II trials of Xenova's P-gp pump inhibitor planned in U.S. and U.K.* DailyDrugNews.com (Daily Essentials) 1998, Dec 16.
8. *Xenova: Q3 1997 highlights*. DailyDrugNews.com (Daily Essentials) 1997, Nov 26.
9. *Xenova: year-end 1997 highlights*. DailyDrugNews.com (Daily Essentials) 1998, March 18.
10. *XR-9576 enters clinical testing*. DailyDrugNews.com (Daily Essentials) 1998, May 12.

*Identified compound **265879** (see **264877**) Drug Data Report 1998, 020(08): 0726.**METABOLIC DRUGS****TREATMENT OF BONE DISEASES****273553**

17 α -Methyl-17-[1-oxo-2-(1-piperazinyl)ethoxy]androst-4-en-3-one



C26 H40 N2 O3; Mol wt: 428.6130

ACTION – Agent for the treatment and prevention of osteoporosis, a steroid-piperazine compound with significant bone growth-promoting activity.

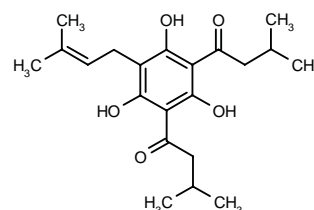
SOURCE – West China University of Medical Sciences, Chengdu (CN).

REFERENCES

1. Zheng, H. et al. *Synthesis and studies on the preliminary bioactivities of steroid-piperazine compounds*. Chin J Med Chem 1998, 8(4): 260.

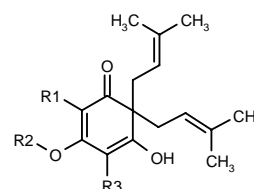
273779

1,1'-[2,4,6-Trihydroxy-5-(3-methyl-2-butenyl)-1,3-phenylene]bis(3-methyl-1-butanone)



C21 H30 O5; Mol wt: 362.4630

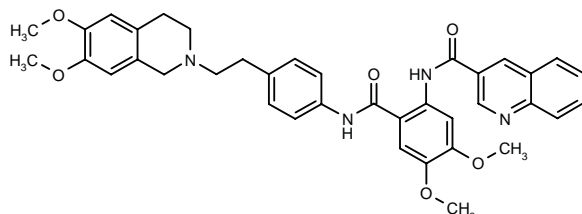
ACTION – Bone resorption inhibitor, as demonstrated by 99.7% inhibition of parathyroid hormone (PTH)-induced bone resorption in murine femoral and tibial bone preparations at 10 μ M. Other compounds from this series of polyhydroxybenzene derivatives include the following:



Compound	R1	R2	R3	Formula
273781	i-BuCO	H	i-BuCO	C ₂₈ H ₃₈ O ₅
273783	H	CH ₂ CH=C(Me) ₂	CH ₂ CH=C(Me) ₂	C ₂₈ H ₃₈ O ₃
273785	CH ₂ CH=C(Me) ₂	H	CH ₂ CH=C(Me) ₂	C ₂₈ H ₃₈ O ₃

XR-9576***265879**

N-[2-[*N*-[4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl)ethyl]phenyl]carbamoyl]-4,5-dimethoxy-phenyl]quinoline-3-carboxamide



C38 H38 N4 O6; Mol wt: 646.7402

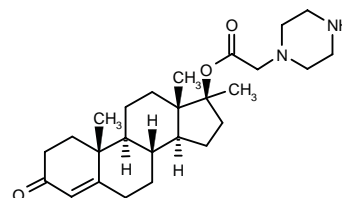
ACTION – Multidrug resistance (MDR) modulator, an anthranilic acid derivative that potentiates the cytotoxic effects of doxorubicin, vincristine, etoposide and paclitaxel against a variety of human and murine P-glycoprotein-expressing MDR cell lines, with IC₅₀ values in the range of 12-40 nM. Compound shows a long duration of action, superior to other MDR modulators such as verapamil and ciclosporin. *In vivo*, compound (5 mg/kg i.v.) significantly enhanced the antitumor activity of doxorubicin in mice with resistant colon carcinoma MC26, and it potentiated the efficacy of etoposide and vincristine in mice with small cell lung carcinoma H69/LX4 xenografts after both oral (6, 12, 245 mg/kg) or i.v. (4, 10 mg/kg) administration. It is in phase II evaluation.

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4. Roe, M. et al. *Reversal of P-glycoprotein mediated multidrug resistance by novel anthranilamide derivatives*. Bioorg Med Chem Lett 1999, 9(4): 595.
5. Stewart, A.J. et al. *An intravenous phase I study with the novel P-glycoprotein-dependent multidrug resistance modulator, XR9576, demonstrates surrogate marker activity in situ*. Proc Amer Soc Clin Oncol 1999, 18: Abst 704.
6. Stewart, A.J. et al. *XR9576, a potent modulator of P-glycoprotein-mediated multidrug resistance*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 556.
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*Identified compound **265879** (see **264877**) Drug Data Report 1998, 020(08): 0726.**METABOLIC DRUGS****TREATMENT OF BONE DISEASES****273553**

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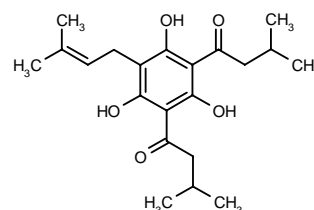
SOURCE – West China University of Medical Sciences, Chengdu (CN).

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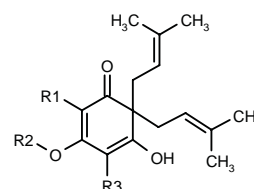
273779

1,1'-[2,4,6-Trihydroxy-5-(3-methyl-2-butenyl)-1,3-phenylene]bis(3-methyl-1-butanone)

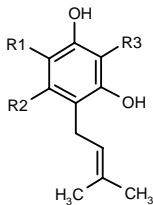


C21 H30 O5; Mol wt: 362.4630

ACTION – Bone resorption inhibitor, as demonstrated by 99.7% inhibition of parathyroid hormone (PTH)-induced bone resorption in murine femoral and tibial bone preparations at 10 μ M. Other compounds from this series of polyhydroxybenzene derivatives include the following:



Compound	R1	R2	R3	Formula
273781	i-BuCO	H	i-BuCO	C ₂₈ H ₃₈ O ₅
273783	H	CH ₂ CH=C(Me) ₂	CH ₂ CH=C(Me) ₂	C ₂₈ H ₃₈ O ₃
273785	CH ₂ CH=C(Me) ₂	H	CH ₂ CH=C(Me) ₂	C ₂₈ H ₃₈ O ₃



Compound	R1	R2	R3	Formula
273782	H	Me	i-BuCO	C ₁₇ H ₂₆ O ₃
273784	CH ₂ CH=C(Me) ₂	OH	CH ₂ CH=C(Me) ₂	C ₂₁ H ₃₀ O ₃

SOURCE – Hoechst Marion Roussel.

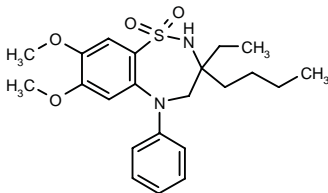
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TREATMENT OF LIPOPROTEIN DISORDERS

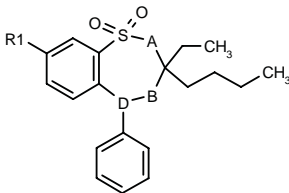
273042

3-Butyl-3-ethyl-7,8-dimethoxy-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine S,S-dioxide



C22 H30 N2 O4 S; Mol wt: 418.5550

ACTION – Hypolipidemic agent that acts by inhibiting bile acid transport (89% inhibition of human bile acid transporter stably expressed in CHO cells at a concentration of 10 μM). Within this series of specifically claimed bicyclic compounds, the following are also included:



Compound	R1	A	B	D	Isomer	Formula
273043	H	NH	CH2	N		C ₂₀ H ₂₆ N ₂ O ₂ S
273044	OMe	NH	CH2	N		C ₂₁ H ₂₈ N ₂ O ₃ S
273045	H	NH	CH2	CH	trans	C ₂₁ H ₂₇ NO ₂ S
273046	OMe	CH2	O	CH	trans	C ₂₂ H ₂₈ O ₄ S

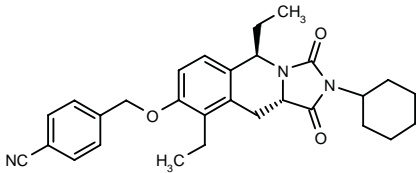
SOURCE – Glaxo Wellcome.

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1. Handlon, A.L. et al. (Glaxo Wellcome plc) *Hypolipidemic bicyclic derivs*. WO 9838182.

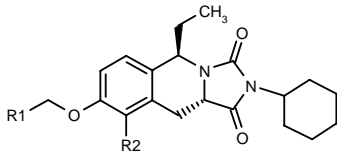
273047

4-[(5*R*,10*aS*)-2-Cyclohexyl-5,9-diethyl-1,3-dioxo-1,2,3,5,10,10*a*-hexahydroimidazo[1,5-*b*]isoquinolin-8-ylloxymethyl]benzonitrile



C29 H33 N3 O3; Mol wt: 471.5977

ACTION – Hypolipidemic and antiatherosclerotic agent, also claimed for use in the treatment of pancreatitis, non-insulin-dependent diabetes mellitus and coronary heart disease, a potent and specific inhibitor of the hepatic production of apolipoprotein B-100 (IC₅₀ = 0.001 μM in HepG2 cells), with good bioavailability and a long duration of action. Within this series of specifically claimed dihydroimidazo[1,5-*b*]isoquinoline-1,3-dione derivatives, the following are also included:



Compound	R1	R2	Formula
273048	4-CN-Ph	Br	C ₂₇ H ₂₈ BrN ₃ O ₃
273049	2-Pyr	Et	C ₂₇ H ₃₃ N ₃ O ₃
273050	2-Pyr	Pr	C ₂₈ H ₃₅ N ₃ O ₃
273051	4-CN-Ph	allyl	C ₃₀ H ₃₃ N ₃ O ₃
273052	4-CN-Ph	Me	C ₂₈ H ₃₁ N ₃ O ₃
273053	2-Pyr	vinyl	C ₂₇ H ₃₁ N ₃ O ₃
273054	2-Pyr	allyl	C ₂₈ H ₃₃ N ₃ O ₃
273055	4-CN-Ph	Pr	C ₃₀ H ₃₅ N ₃ O ₃

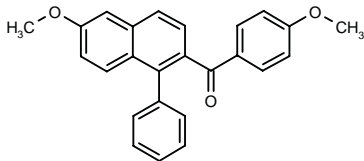
SOURCE – Glaxo Wellcome.

REFERENCES

1. Sierra, M.L. and Pianetti, P.M.C. (Glaxo Group Ltd.) *Dihydroimidazo[1,5-*b*]isoquinoline-1,3-diones as apoprotein B-100 inhibitors*. WO 9856790.

273160

1-(4-Methoxyphenyl)-1-(6-methoxy-1-phenyl-2-naphthyl)-methanone



C25 H20 O3; Mol wt: 368.4300

ACTION – Agent for the treatment of hyperlipidemia, particularly hypercholesterolemia, that is reported to act by downregulating the expression of hepatic lipase, an enzyme that controls the degradation of HDL particles, thus leading to increased HDL levels. Preferably for use in postmenopausal women. In ovariectomized rats, compound was shown to decrease serum cholesterol levels by 75.3% at 0.1 mg/kg/day p.o. x 4 days, being comparable in potency to 17 α -ethinylestradiol (78.4% decrease at 0.1 mg/kg/day p.o. x 4 days).

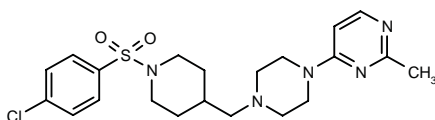
SOURCE – Lilly.

REFERENCES

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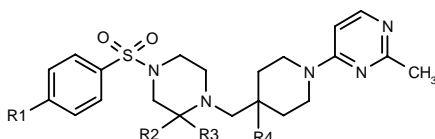
273580

4-[4-[1-(4-Chlorophenylsulfonyl)-4-piperidinylmethyl]-1-piperazinyl]-2-methylpyrimidine

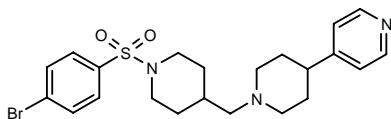


C21 H28 Cl N5 O2 S; Mol wt: 450.0042

ACTION – Hypolipidemic and antiatherosclerotic agent that inhibits cholesterol biosynthesis by virtue of its ability to inhibit lanosterol synthase activity. Within this series of pyridyl- and pyrimidyl-heterocyclic compounds, the following are also included:



Compound	R1	R2	R3	R4	Formula
273582	CF ₃	H	H	H	C ₂₂ H ₂₈ F ₃ N ₅ O ₂ S
273583	CF ₃	H	H	OH	C ₂₂ H ₂₈ F ₃ N ₅ O ₃ S
273584	Br	-O-		H	C ₂₁ H ₂₆ BrN ₅ O ₃ S



273581: C₂₂ H₂₈ Br N₃ O₂ S

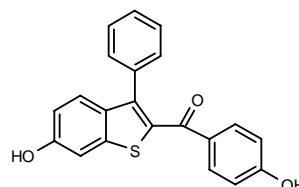
SOURCE – Zeneca (AstraZeneca).

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1. Newcombe, N.J. and Johnson, M.C. (Zeneca Ltd.) *Pyridyl- and pyrimidyl-heterocyclic cpds. inhibiting oxido squalene-cyclase*. WO 9906395.

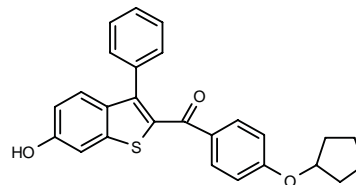
273714

1-(4-Hydroxyphenyl)-1-(6-hydroxy-3-phenylbenzo-[b]thiophen-2-yl)methanone



C₂₁ H₁₄ O₃ S; Mol wt: 346.4046

ACTION – Agent for the treatment of hyperlipidemia, particularly hypercholesterolemia, that acts by downregulating the expression of hepatic lipase, an enzyme that controls the degradation of HDL particles, thus leading to an increase in HDL levels. *In vivo*, it was found to dose-dependently decrease hepatic lipase activity and plasma cholesterol and triglyceride levels at day 4 when given at 10-1000 mg/kg/day p.o. x 4 days to rats. Preferably for use in postmenopausal women. Another compound from this series of benzo[b]thiophene derivatives is:



273715: C₂₆ H₂₂ O₃ S

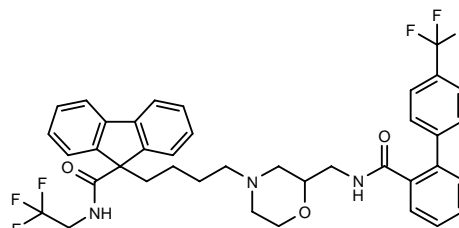
SOURCE – Lilly.

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273728

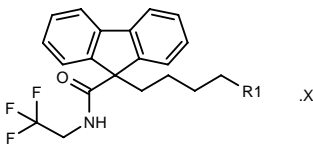
N-(2,2,2-Trifluoroethyl)-9-[4-[2-[4'-(trifluoromethyl)-biphenyl-2-ylcarboxamidomethyl]-4-morpholinyl]butyl]-9H-fluorene-9-carboxamide hydrochloride



.HCl

C₃₉ H₃₇ F₆ N₃ O₃ . HCl; Mol wt: 746.1882

ACTION – Agent for the treatment of atherosclerosis and hyperlipidemia, an inhibitor of microsomal triglyceride transfer protein (MTP) and of apolipoprotein B (ApoB) secretion (IC₅₀ = 0.0150 μ M in HepG2 cells). Other compounds from this series of cyclic amine derivatives include the following:



Compound	R1	X	Formula
273729	3-[2-(4-CF3-Ph)-Ph-CON(Me)CH2]-1-Pip		C ₄₁ H ₄₁ F ₆ N ₃ O ₂
273730	3-[2-(4-CF3-Ph)-Ph-CONHCH2]-1-azetidiny		C ₃₈ H ₃₅ F ₆ N ₃ O ₂
273731	2-[2-(4-CF3-Ph)-Ph-CONHCH2]-1-pyrrolidiny		C ₃₉ H ₃₇ F ₆ N ₃ O ₂
273732	3-(1,1,3-trioxo-2,3-dihydro-2-benzisothiazolyl-CH2)-1-Pip	HCl	C ₃₃ H ₃₄ F ₃ N ₃ O ₄ S.HCl

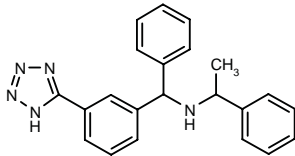
SOURCE – Wakunaga.

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1. Inoue, S. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Aminomethyl cyclic amine cpds. and medicines containing them.* JP 99035555.

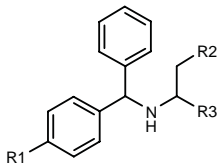
273861

N-(1-Phenylethyl)-N-[1-phenyl-1-[3-(1H-tetrazol-5-yl)-phenyl]methyl]amine



C22 H21 N5; Mol wt: 355.4429

ACTION – Hypolipidemic agent, an ileal bile acid transport inhibitor. *In vitro*, compound inhibited [³H]-taurocholic acid uptake into Caco-2 cells expressing the ileal transporter (IC₅₀ = 2.1 µg/ml), as well as into rat ileal rings (77% inhibition at 100 µg/ml). A representative compound from a series of benzylamine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
273883	4-Me-PhSO2NHCONH	H	Ph	C ₂₉ H ₂₉ N ₃ O ₃ S
273885	4-Me-PhSO2NHCONH	H	Ph	C ₂₉ H ₂₉ N ₃ O ₃ S
273890	5-tetrazolyl	Pr	Et	C ₂₁ H ₂₇ N ₅
273891	5-tetrazolyl	H	cyclohexyl	C ₂₂ H ₂₇ N ₅

SOURCE – Sankyo.

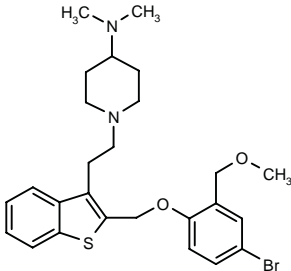
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

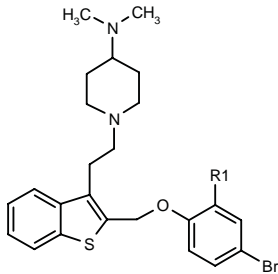
272684

2-[4-Bromo-2-(methoxymethyl)phenoxyethyl]-3-[2-[4-(dimethylamino)piperidin-1-yl]ethyl]benzothiophene



C26 H33 Br N2 O2 S; Mol wt: 517.5287

ACTION – Neuropeptide Y (NPY) Y₁ receptor antagonist with high affinity for cloned human Y₁ receptors (K_i = 11 nM). Potentially useful for the treatment of obesity and type II diabetes. Other compounds from this series of benzothiophene-derived NPY Y₁ antagonists include the following:



Compound	R1	Formula
272683	CH2OH	C ₂₅ H ₃₁ BrN ₂ O ₂ S
272685	CN	C ₂₅ H ₂₈ BrN ₃ OS

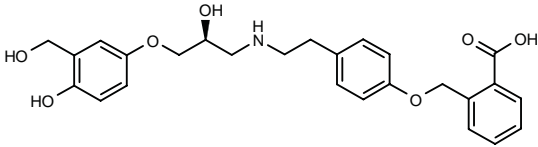
SOURCE – Lilly.

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1. Britton, T.C. et al. *Structure-activity relationships of a series of benzothiophene-derived NPY Y1 antagonists: Optimization of the C-2 side chain.* Bioorg Med Chem Lett 1999, 9(3): 475.

272742

2-[4-[2-[2(S)-Hydroxy-3-[4-hydroxy-3-(hydroxymethyl)-phenoxy]propylamino]ethyl]phenoxyethyl]benzoic acid



C26 H29 N O7; Mol wt: 467.5151

ACTION – Antiobesity agent, a potent β₃-adrenoceptor agonist (EC₅₀ = 1.3 µM) with selectivity relative to β₁- and β₂-adrenoceptors (K_i = 30 and 10 µM against cloned human β₁- and β₂-adrenoceptors, respectively).

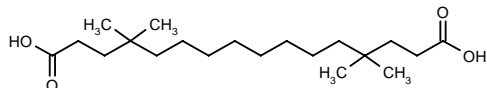
SOURCE – SmithKline Beecham.

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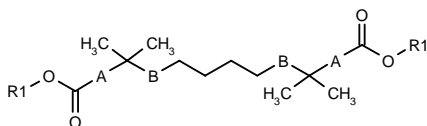
273232

4,4,13,13-Tetramethylhexadecanedioic acid



C20 H38 O4; Mol wt: 342.5162

ACTION – Agent for the treatment of obesity, hyperlipidemia, impaired glucose tolerance and non-insulin-dependent diabetes mellitus proven to potently decrease plasma triglyceride, plasma apolipoprotein C-III and plasma insulin levels when given orally to rats mixed with the diet at a concentration of 0.1%, while having no effect on food intake. When tested *in vitro* in isolated hepatocytes, compound was found to produce a decrease in mitochondrial membrane potential, leading to an increase in calorogenesis. Other specifically claimed compounds from this series of dicarboxylic acid derivatives include the following:



Compound	R1	A	B	Formula
273233	H	-(CH2)2-	-CH2-	C ₁₈ H ₃₄ O ₄
273234	Et	-CH=CH-	-CH=CH-	C ₂₄ H ₃₈ O ₄
273235	H	-(CH2)2-	-(CH2)3-	C ₂₂ H ₄₂ O ₄
273236	H	bond	-(CH2)4-	C ₂₀ H ₃₈ O ₄
273237	H	bond	-(CH2)5-	C ₂₂ H ₄₂ O ₄

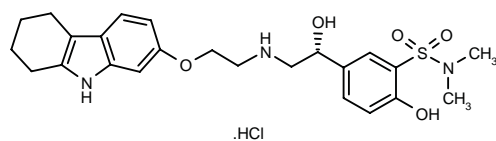
SOURCE – Yissum.

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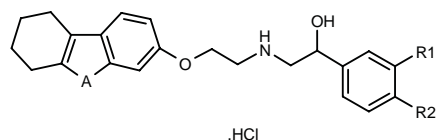
273399

2-Hydroxy-5-[1(*R*)-hydroxy-2-[2-(6,7,8,9-tetrahydro-5*H*-carbazol-2-yloxy)ethylamino]ethyl]-*N,N*-dimethylbenzenesulfonamide hydrochloride



C24 H31 N3 O5 S . HCl; Mol wt: 510.0518

ACTION – Agent for the treatment of obesity, diabetes and hyperlipidemia, a β_3 -adrenoceptor agonist, as demonstrated by stimulation of cAMP in CHO cells transfected with the human β_3 -adrenoceptor (EC_{50} = 0.26 nM; 63% activation vs. isoproterenol) and by stimulation of rat adipocyte lipolysis (EC_{50} = 2000 nM; 127% activation vs. isoproterenol). It also demonstrated hypoglycemic effects in mice at 10 mg/kg i.p. No mortality was observed following oral administration of a dose of 100 mg/kg to mice. Other tricyclic compounds include the following:



Compound	R1	R2	A	Isomer	Formula
273400	NHSO2Me	OCH2Ph	NH	R	C ₃₀ H ₃₅ N ₃ O ₅ S.HCl
273401	NHSO2Me	OH	NH	R	C ₂₃ H ₂₉ N ₃ O ₅ S.HCl
273402	NHSO2Me	F	NH	R	C ₂₃ H ₂₈ FN ₃ O ₄ S.HCl
273403	NHSO2Me	Cl	NH	racemic	C ₂₃ H ₂₈ ClN ₃ O ₄ S.HCl
273404	NHSO2Me	Br	NH	R	C ₂₃ H ₂₈ BrN ₃ O ₄ S.HCl
273405	NHSO2Me	H	NH	racemic	C ₂₃ H ₂₉ N ₃ O ₄ S.HCl
273406	SO2N(Me)2	OH	O	R	C ₂₄ H ₃₀ N ₂ O ₆ S.HCl
273407	NHSO2Me	OH	O	R	C ₂₃ H ₂₈ N ₂ O ₆ S.HCl
273408	NHSO2Me	OH	S	R	C ₂₃ H ₂₈ N ₂ O ₅ S ₂ .HCl

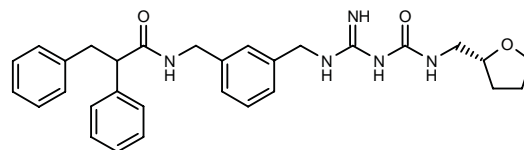
SOURCE – Asahi Chemical.

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273788

N-[*N*-[3-(2,3-Diphenylpropionamidomethyl)benzyl]-amidino]-*N'*-[tetrahydrofuran-2(*R*)-ylmethyl]urea



C30 H35 N5 O3; Mol wt: 513.6385

ACTION – Potent neuropeptide Y (NPY) Y_1 receptor antagonist (IC_{50} = 35 nM against [¹²⁵I]-PYY binding to NPY receptors in human neuroblastoma SK-N-MC cell membranes). *In vivo*, compound (30 nmol) significantly attenuated feeding in fasted rats.

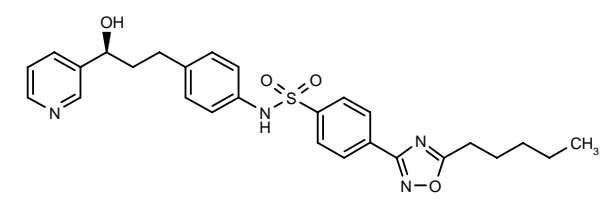
SOURCE – Alanex.

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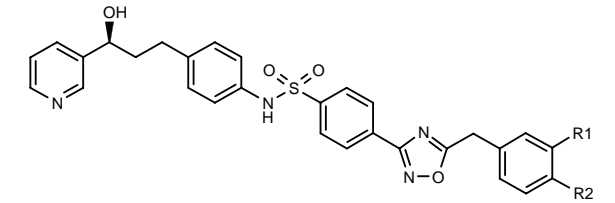
273789

N-[4-[3(*S*)-Hydroxy-3-(3-pyridinyl)propyl]phenyl]-4-(5-pentyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide



C27 H30 N4 O4 S; Mol wt: 506.6240

ACTION – Potent, selective and orally active β_3 -adrenoceptor agonist (EC_{50} = 23 nM), potentially useful for the treatment of metabolic diseases such as obesity and type II diabetes. Other related oxadiazole benzenesulfonamides include the following:



Compound	R1	R2	Formula
273790	F	F	C ₂₉ H ₂₄ F ₂ N ₄ O ₄ S
273791	H	OCF3	C ₃₀ H ₂₅ F ₃ N ₄ O ₅ S

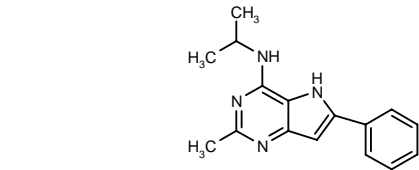
SOURCE – Merck & Co.

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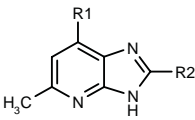
273868

N-Isopropyl-N-(2-methyl-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amine

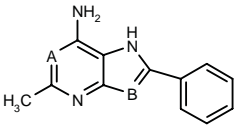


C16 H18 N4; Mol wt: 266.3462

ACTION – Neuropeptide Y (NPY) receptor antagonist with potential in the treatment of eating disorders, cardiovascular disorders, cerebral disorders, sexual dysfunction and respiratory disorders. Within this series of 4-amino-pyrrolo[3,2-*d*]pyrimidines, the following are also specifically claimed:



Compound	R1	R2	Formula
273869	1-pyrrolidinyl	cyclohexyl	C ₁₇ H ₂₄ N ₄
273870	OMe	Ph	C ₁₄ H ₁₃ N ₃ O
273871	1-pyrrolidinyl	4-Pyr	C ₁₆ H ₁₇ N ₅



Compound	R1	A	B	Formula
273872	2(S)-(MeOCH2)-1-pyrrolidinyl	N	CH	C ₁₉ H ₂₂ N ₄ O
273873	1-Pip	CH	N	C ₁₈ H ₂₀ N ₄
273874	2(R)-(MeOCH2)-1-pyrrolidinyl	N	CH	C ₁₉ H ₂₂ N ₄ O

SOURCE – Pfizer.

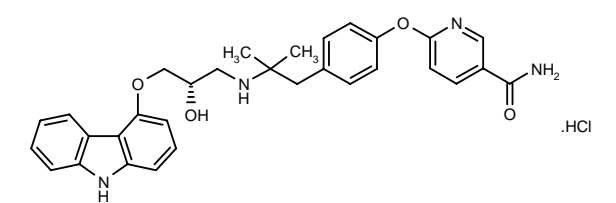
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LY-377604

273793

6-[4-[2-[3-(9*H*-Carbazol-4-yloxy)-2(*S*)-hydroxypropyl-amino]-2-methylpropyl]phenoxy]pyridine-3-carboxamide hydrochloride



C31 H32 N4 O4 . HCl; Mol wt: 561.0787

ACTION – Potent and selective human β_3 -adrenoceptor agonist (IC_{50} = 4.3 nM) with antagonist activity at β_1 - and β_2 -adrenoceptors. In obese male Zucker rats, compound reduced body weight without reducing food intake, and increased energy expenditure. Such a profile is expected to be particularly useful for the treatment of metabolic syndrome, i.e., obesity, diabetes and cardiovascular disease.

SOURCE – Lilly.

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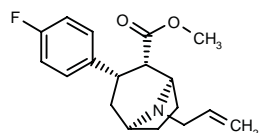
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DIAGNOSTIC AGENTS

ALTROPANE

233807

(1*R*,2*S*,3*S*,5*S*)-3-(4-Fluorophenyl)-8-(2-propenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C₁₈ H₂₂ F N O₂; Mol wt: 303.3748

ACTION – Imaging agent for the dopamine transporter (DAT) system in the brain with binding, brain distribution and pharmacological properties suitable for SPECT (single-photon emission computed tomography) scan diagnosis of Parkinson's disease, entering phase III trials.

SOURCES – Boston Life Sciences; Organix.

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18. Boston Life Sciences announces results of phase I/II study on Altoprane. Boston Life Sciences Inc. Press Release 1996, July 16.

19. Boston Life Sciences to begin clinical trials with Altoprane. Boston Life Sciences Inc. Press Release 1997, Jan 13.

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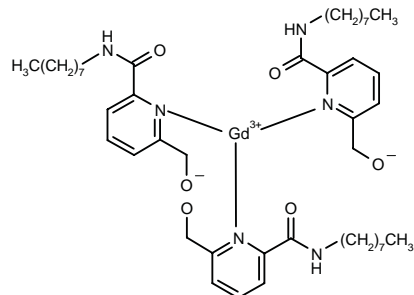
26. Boston Life Sciences Inc. Product Pipeline 1996, Jan 12.

Gd-TOCAPM

272635

Tris[[6-(*N*-octylcarbamoyl)-2-pyridinyl]methanolate-(1-)]-gadolinium

GdTOCAPM



3 C₁₅ H₂₃ Gd N₂ O₂; Mol wt: 947.3261

ACTION – Gadolinium complex for use as a contrast agent in magnetic resonance imaging (MRI) and X-ray imaging procedures.

SOURCE – Hoechst Celanese.

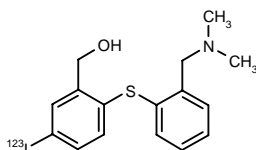
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[¹²³I]-IDAM

273101

5-[¹²³I]-Iodo-2-[2-(*N,N*-dimethylaminomethyl)phenyl-sulfanyl]benzylalcohol



C16 H18 I N O S; Mol wt: 395.3902

ACTION – Radioiodinated tracer for *in vivo* study of 5-HT reuptake or transporter sites (SERT), with high binding affinity for SERT ($K_i = 0.097$ nM) and rapid brain uptake, particularly in the hypothalamus, and washout. Preliminary imaging studies on baboon brain using SPECT (single-photon emission computed tomography) with compound injected i.v. demonstrated (at 60 and 120 min after injection) an excellent contrast in midbrain areas where SERTs are found in high density.

SOURCE – University of Pennsylvania, Philadelphia, PA (US).

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NC-100100

209720

Isotonic formulation of flexible stabilized perfluorocarbon-filled microbubbles with a median diameter of 3-5 μm

Sonazoid™

ACTION – Echocardiographic contrast agent for use in patients with ischemic heart disease and liver disease. In dogs, compound given i.v. generated myocardial contrast enhancement allowing identification of myocardial perfusion abnormalities during acute coronary occlusion and myocardial reperfusion after thrombolysis. Compound is currently in phase II clinical trials.

SOURCES – Daiichi Pharmaceutical; Nycomed Amersham.

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SIMETHICONE-COATED CELLULOSE

217607

Simethicone-coated cellulose suspension, 7.5 mg/ml

ACTION – Diagnostic ultrasound imaging agent that acts locally within the gastrointestinal tract to adsorb and disperse gas within the bowel lumen, reducing gas shadowing.

INDICATION – To enhance the delineation of upper abdominal anatomy in conjunction with ultrasound imaging.

PRESENTATION – Single-dose bottles containing an aqueous suspension (400 ml), 7.5 mg/ml.

PROPRIETARY NAME – SonoRx (US).

SOURCES – Bracco (licensed from ImaRx); manufactured by Bristol-Myers Squibb.

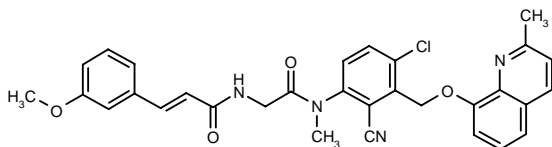
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2. Lev-Toaff, A.S. et al. *The utility of SonoRx, a new oral ultrasound contrast agent, in patients evaluated for suspected upper abdominal pathology*. Gastroenterology 1995, 108(4, Suppl.): A23.
3. Lev-Toaff, A.S. et al. *Use of simethicone-coated cellulose suspension to improve pancreatic ultrasound: Experience in 55 patients with pancreatic pathology*. 84th Annu Meet Radiol Soc North Am (RSNA) (Nov 29-Dec 4, Chicago) 1998, Abst.
4. Spinazzi, A. et al. *Clinical evaluation of SonoRx®, an oral ultrasound contrast agent in patients with suspected abdominal pathology: Comparison with oral water*. Eur Cong Radiol (March 7-12, Vienna) 1999, Abst 130.
5. *Bracco launches new ultrasound image-enhancing agent in U.S.* DailyDrugNews.com (Daily Essentials) 1999, Feb 23.
6. *New developments in contrast agents*. Medpro Month 1994, 4(11-12): 203.
7. *New oral ultrasound contrast agent approved by FDA*. DailyDrugNews.com (Daily Essentials) 1998, Nov 17.
8. Bracco Diagnostics, Inc. Product Fact Sheet 1994, Dec 16.

PHARMACOLOGICAL TOOLS

272670

N-[2-[*N*-[4-Chloro-2-cyano-3-(2-methylquinolin-8-yloxy-methyl)phenyl]-*N*-methylamino]-2-oxoethyl]-3-methoxycinnamamide



C31 H27 Cl N4 O4; Mol wt: 555.0313

ACTION – Potent bradykinin B₂ receptor antagonist from a series of *O*-substituted 8-quinolines and 4-benzothiazoles, with subnanomolar affinity for the receptor (K_i = 0.1 nM, IC_{50} = 0.7 nM for inhibition of [³H]-bradykinin binding to guinea pig ileum membrane preparations). In a functional assay, compound inhibited bradykinin-induced vasoconstriction in isolated guinea pig ileum with an EC_{50} of 4.1 nM. Potentially useful as a pharmacological tool for elucidating the physiological and pathophysiological role of the B₂ receptor.

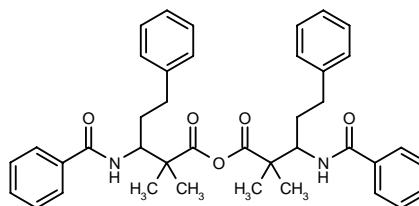
SOURCE – Hoechst Marion Roussel.

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1. Heitsch, H. et al. (Hoechst AG) *Fused N-heterocyclic cpds. substd. with benzyloxy, process for their preparation and their use as bradykinin receptor antagonists*. EP 867432, JP 98279563.
2. Heitsch, H. et al. *Novel series of O-substituted 8-quinolines and 4-benzothiazoles as potent antagonists of the bradykinin B₂ receptors*. Bioorg Med Chem Lett 1999, 9(3): 327.

272676

(-)-2,2-Dimethyl-5-phenyl-3-(benzamido)pentanoic acid anhydride



C40 H44 N2 O5; Mol wt: 632.7966

ACTION – Potent human chymase inhibitor (IC_{50} = 5.6 nM) with some selectivity over bovine pancreatic α -chymotrypsin, human cathepsin G, porcine pancreatic elastase and porcine pancreatic trypsin (IC_{50} = 12, 21, 3300 and 1200 nM, respectively). Compound interacts in a competitive manner with the active site of chymase and forms a stable acyl-enzyme; the estimated K_i value against hamster chymase was 145 nM.

SOURCE – Nippon Steel.

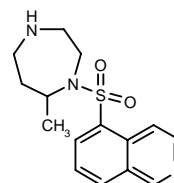
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HMN-1180

261672

5-(7-Methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline



C15 H19 N3 O2 S; Mol wt: 305.4001

ACTION – Specific inhibitor of neuronal nitric oxide synthase (nNOS; K_i = 5.4 μ M) that competes with L-arginine but not calmodulin for the substrate binding site of the enzyme. Compound had no significant inhibitory effect up to concentrations of 100 μ M against inducible NOS (iNOS) and endothelial NOS (eNOS). In the human neuroblastoma SK-N-MC cell line, it significantly inhibited glutamate-induced NO production (nNOS-dependent) at a concentration of 100 μ M, suggesting its ability to cross the cell membrane. Potentially useful as a pharmacological tool for elucidating the physiological role of nNOS.

INDICATION – To enhance the delineation of upper abdominal anatomy in conjunction with ultrasound imaging.

PRESENTATION – Single-dose bottles containing an aqueous suspension (400 ml), 7.5 mg/ml.

PROPRIETARY NAME – SonoRx (US).

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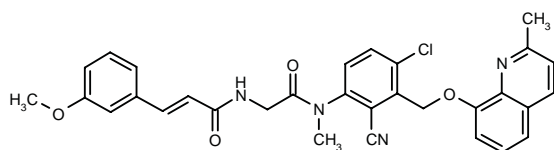
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PHARMACOLOGICAL TOOLS

272670

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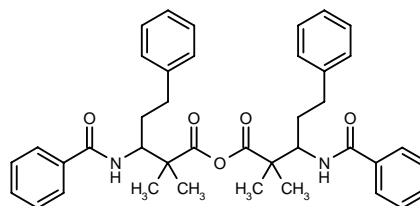
SOURCE – Hoechst Marion Roussel.

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272676

(-)-2,2-Dimethyl-5-phenyl-3-(benzamido)pentanoic acid anhydride



C40 H44 N2 O5; Mol wt: 632.7966

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SOURCE – Nippon Steel.

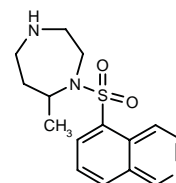
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1. Iijima, K. et al. *Symmetrical anhydride-type serine protease inhibitors: Structure-activity relationship studies of human chymase inhibitors*. Bioorg Med Chem Lett 1999, 9(3): 413.

HMN-1180

261672

5-(7-Methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline



C15 H19 N3 O2 S; Mol wt: 305.4001

ACTION – Specific inhibitor of neuronal nitric oxide synthase (nNOS; K_i = 5.4 μ M) that competes with L-arginine but not calmodulin for the substrate binding site of the enzyme. Compound had no significant inhibitory effect up to concentrations of 100 μ M against inducible NOS (iNOS) and endothelial NOS (eNOS). In the human neuroblastoma SK-N-MC cell line, it significantly inhibited glutamate-induced NO production (nNOS-dependent) at a concentration of 100 μ M, suggesting its ability to cross the cell membrane. Potentially useful as a pharmacological tool for elucidating the physiological role of nNOS.

SOURCE – Nagoya University, Nagoya (JP).

REFERENCES

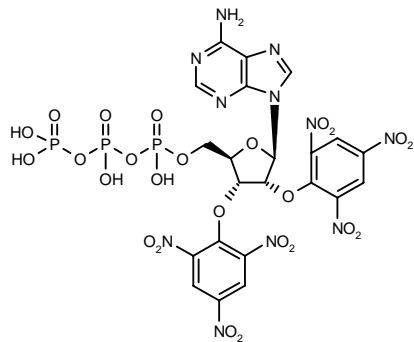
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TNP-ATP

272848

2',3'-Bis-O-(2,4,6-trinitrophenyl)adenosine 5'-triphosphate



C22 H18 N11 O25 P3; Mol wt: 929.3582

ACTION – Potent P2X receptor antagonist with an IC₅₀ of approx. 2 nM for inhibition of P2X-mediated inward currents in rat mesenteric artery smooth muscle cells. Compound exhibited weak, nonselective antagonism of α,β-MeATP-induced contractions in mesenteric artery rings, with an IC₅₀ of about 30 μM, indicating probable metabolic breakdown in whole tissue preparations.

SOURCE – Glaxo Wellcome.

REFERENCES

1. Lewis, C.J. et al. *2',3'-O-(2,4,6-trinitrophenyl) adenosine 5'-triphosphate (TNP-ATP)-a nanomolar affinity antagonist at rat mesenteric artery P2X receptor ion channels*. Br J Pharmacol 1998, 124(7): 1463.

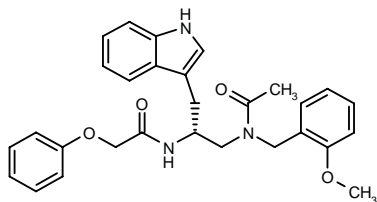
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

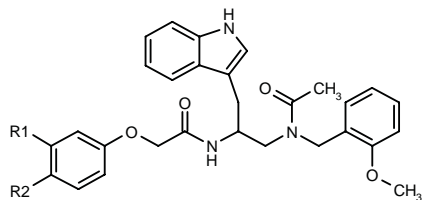
273718

N-[2-[*N*-Acetyl-*N*-(2-methoxybenzyl)amino]-1-(*R*)-(1*H*-indol-3-ylmethyl)ethyl]-2-phenoxyacetamide



C29 H31 N3 O4; Mol wt: 485.5809

ACTION – Tachykinin receptor antagonist with potential in the treatment of a broad range of disorders including CNS disorders such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as Alzheimer's disease and Down's syndrome; respiratory diseases such as asthma and bronchospasm; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; immunological disorders such as transplant rejection; gastrointestinal disorders such as irritable bowel syndrome; incontinence; and pain. Other compounds from this series of 2-acylaminopropanamines include the following:



Compound	R1	R2	Isomer	Formula
273719	H	CH2CH2CO2Me	R	C ₃₃ H ₃₇ N ₃ O ₆
273720	H	CH2OH	R	C ₃₀ H ₃₃ N ₃ O ₅
273721	H	CH2CH2OMe		C ₃₂ H ₃₇ N ₃ O ₅
273722		-S-CH=N-		C ₃₀ H ₃₀ N ₄ O ₄ S
273723	CH2CH2OH	H		C ₃₁ H ₃₅ N ₃ O ₅
273724	H	1,2,3-thiadiazol-4-yl		C ₃₁ H ₃₁ N ₅ O ₄ S

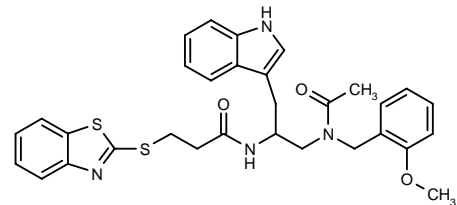
SOURCE – Lilly.

REFERENCES

1. Fritz, J.E. et al. (Eli Lilly and Company) 2-Acylaminopropanamines as tachykinin receptor antagonists. WO 9907677.

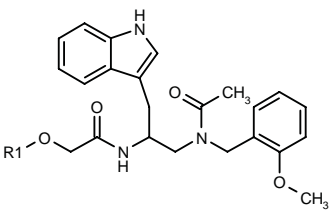
273725

N-[2-[*N*-Acetyl-*N*-(2-methoxybenzyl)amino]-1-(1*H*-indol-3-ylmethyl)ethyl]-3-(benzothiazol-2-ylsulfanyl)propionamide



C31 H32 N4 O3 S2; Mol wt: 572.7508

ACTION – Nonpeptide tachykinin receptor antagonist, potentially useful in the treatment or prevention of conditions associated with excess tachykinins, e.g., pain, inflammatory disorders, urinary incontinence and CNS disorders. Other exemplified compounds within this series of 2-acylaminopropanamines include the following:



Compound	R1	Formula
273726	6-quinolyl	C ₃₂ H ₃₂ N ₄ O ₄
273727	2-Pyr	C ₂₈ H ₃₀ N ₄ O ₄

SOURCE – Lilly.

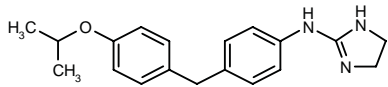
REFERENCES

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274400

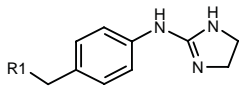
N-[4-(4-Isopropoxybenzyl)phenyl]-4,5-dihydro-1*H*-imidazol-2-amine

N-(4,5-Dihydro-1*H*-imidazol-2-yl)-*N*-[4-(4-isopropoxybenzyl)phenyl]amine



C19 H23 N3 O; Mol wt: 309.4107

ACTION – Prostaglandin I₂ (PGI₂) IP receptor antagonist with potential in the treatment of pain, inflammation, urinary incontinence, asthma and septic shock. Other specifically claimed compounds from this series of 2-(phenylamino)imidazoline derivatives include the following:



Compound	R1	Formula
274401	4-(2-THP-O)-Ph	C ₂₁ H ₂₅ N ₃ O ₂
274402	2-F-4-(4-THP-CH2O)-Ph	C ₂₂ H ₂₆ FN ₃ O ₂
274403	4-(cyclopentyl-O)-2-thienyl	C ₁₉ H ₂₃ N ₃ OS
274404	4-(4-MeO-PhSO2CH2NHCH2CH2O)-Ph	C ₂₆ H ₃₀ N ₄ O ₄ S
274406	4-(BuNHSO2)-Ph	C ₂₀ H ₂₆ N ₄ O ₂ S
274407	4-(PhCH2NHCO)-Ph	C ₂₄ H ₂₄ N ₄ O

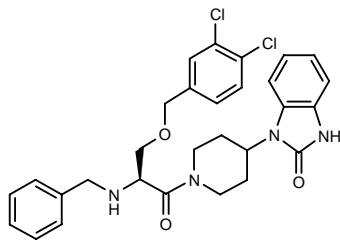
SOURCE – Roche.

REFERENCES

1. Bley, K.R. et al. (F. Hoffmann-La Roche AG) *2-(Arylphenyl)amino-imidazoline derivs.* EP 902018.

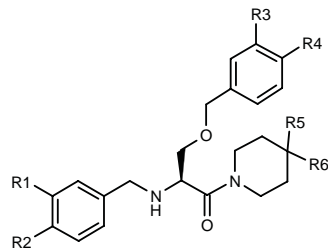
274532

1-[1-[2(*S*)-(Benzylamino)-3-(3,4-dichlorobenzoyloxy)-propionyl]-4-piperidiny]-2,3-dihydro-1*H*-benzimidazol-2-one

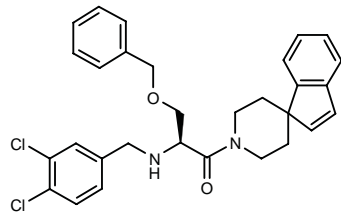


C29 H30 Cl2 N4 O3; Mol wt: 553.4870

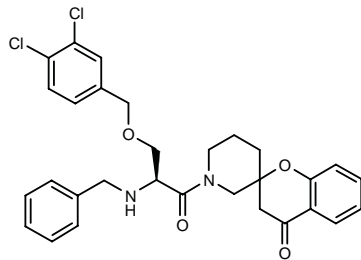
ACTION – Agent for the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia, a tachykinin, especially substance P (NK₁ receptor), antagonist. Within this series of specifically claimed serine derivatives, the following are also included:



Compound	R1=R2	R3=R4	R5	R6	Formula
274535	Cl	H	CH2NHSO2Me	Ph	C ₃₀ H ₃₅ Cl ₂ N ₃ O ₄ S
274536	H	Cl	CO2Me	Ph	C ₃₀ H ₃₂ Cl ₂ N ₂ O ₄
274537	H	Cl	2-[MeSO2N(Me)]-Ph	H	C ₃₀ H ₃₅ Cl ₂ N ₃ O ₄ S
274539	H	Cl	CH2N(Ph)SO2Me	H	C ₃₀ H ₃₅ Cl ₂ N ₃ O ₄ S



274533: C30 H30 Cl2 N2 O2



274540: C30 H30 Cl2 N2 O4

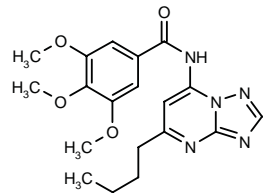
SOURCE – Merck Sharp & Dohme.

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1. Elliott, J.M. et al. (Merck Sharp & Dohme Ltd.) *Serine derivs. and their use as therapeutic agents.* US 5885999.

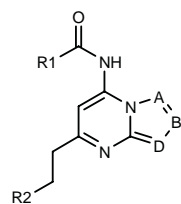
274553

N-(5-Butyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-3,4,5-trimethoxybenzamide



C19 H23 N5 O4; Mol wt: 385.4217

ACTION – Analgesic agent active against substance P-induced pain in rats at 1 mg/kg p.o. A representative compound from a series of fused pyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	A	B	D	Formula
274554	3,4,5-(MeO)3-Ph	Et	CH	N	C(CN)	C ₂₁ H ₂₃ N ₅ O ₄
274555	2-Me-Ph	Et	N	CH	N	C ₁₇ H ₁₉ N ₅ O
274556	3,4,5-(MeO)3-Ph	H	N	CH	N	C ₁₇ H ₁₉ N ₅ O ₄
274557	2-Cl-Ph	Et	N	CH	N	C ₁₆ H ₁₆ ClN ₅ O
274558	2-CF ₃ -Ph	Et	CH	N	C(CN)	C ₁₉ H ₁₆ F ₃ N ₅ O
274559	2,4-(Cl)2-Ph	Et	CH	N	C(CN)	C ₁₈ H ₁₅ Cl ₂ N ₅ O
274560	1-Naph	Et	CH	N	C(CN)	C ₂₂ H ₁₉ N ₅ O
274561	4-MeS-Ph	Et	N	CH	N	C ₁₇ H ₁₉ N ₅ OS

Some compounds within the scope of the invention are also reported to possess inducible nitric oxide synthase (NOS)-inhibitory activity.

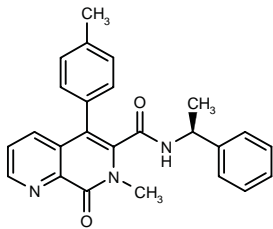
SOURCE – Otsuka.

REFERENCES

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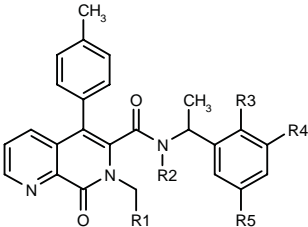
274693

7-Methyl-5-(4-methylphenyl)-8-oxo-*N*-[1(*S*)-phenylethyl]-7,8-dihydro[1,7]naphthyridine-6-carboxamide



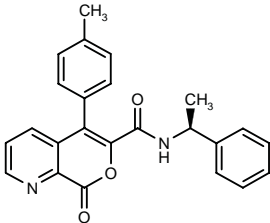
C25 H23 N3 O2; Mol wt: 397.4757

ACTION – Tachykinin NK₁ receptor antagonist, a representative compound from a series of heterocyclic derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4=R5	Isomer	Formula
274694	H	Me	H	H	S	C ₂₆ H ₂₅ N ₃ O ₂
274696	(CH ₂) ₃ OH	H	H	H	S	C ₂₈ H ₂₉ N ₃ O ₃
274697	-(CH ₂) ₃ -	H	H	H	S	C ₂₈ H ₂₇ N ₃ O ₂
274698	H	H	H	CF ₃	S	C ₂₇ H ₂₁ F ₆ N ₃ O ₂
274699	H	H	H	CF ₃	R	C ₂₇ H ₂₁ F ₆ N ₃ O ₂
274700	H	Me	H	CF ₃	R	C ₂₈ H ₂₃ F ₆ N ₃ O ₂

Compound	R1	R2	R3	R4=R5	Isomer	Formula
274701	H	H	H	OMe	racemic	C ₂₇ H ₂₇ N ₃ O ₄
274702	H	Me	H	OMe	racemic	C ₂₈ H ₂₉ N ₃ O ₄
274703	H	H	OMe	H	racemic	C ₂₆ H ₂₅ N ₃ O ₃
274704	H	Me	OMe	H	racemic	C ₂₇ H ₂₇ N ₃ O ₃



274695: C₂₄ H₂₀ N₂ O₃

SOURCE – Takeda.

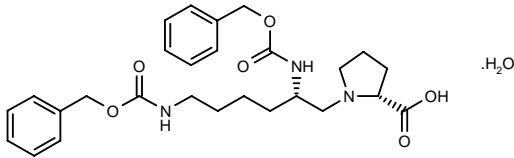
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1. Natsugari, H. and Ikeura, Y. (Takeda Chemical Industries, Ltd.) *Heterocyclic cpds., their preparation method and agents.* JP 99043489.

274782

N-[2(*S*),6-Bis(benzyloxycarboxamido)hexyl]-*D*-proline hydrate

*N*²,*N*⁶-Bis(benzyloxycarbonyl)-*L*-lysyl-[ψCH₂N]-*D*-proline hydrate



C27 H35 N3 O6 . H₂O; Mol wt: 515.6033

ACTION – Analgesic agent, a nonpeptide derivative of IL-1β(193-195) sequence proven to be more potent than indomethacin and morphine in the rat inflamed paw pressure test (IC₅₀ = 0.0035, 0.22 and 0.75 mg/kg i.p., respectively). Compound showed weak antiinflammatory activity in the rat carrageenan-induced paw edema model and was inactive in the mouse hot-plate test.

SOURCE – Molteni.

REFERENCES

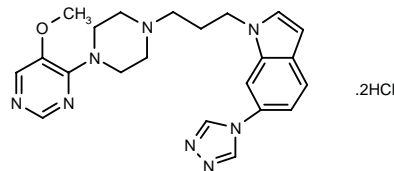
1. Adem bri, G. et al. (Molteni & C. SpA) *Amines exhibiting analgesic action, their preparation and use.* WO 9633210.

2. Fantetti, L. et al. *Synthesis and antinociceptive activity of some novel nonpeptide derivatives of interleukin-1β (193-195) sequence.* *Arzneim-Forsch Drug Res* 1999, 49(2): 137.

ANTIMIGRAINE DRUGS

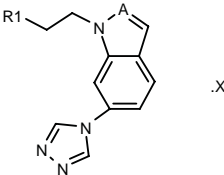
274394

1-[3-[4-(5-Methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-6-(4*H*-1,2,4-triazol-4-yl)-1*H*-indole dihydrochloride



C22 H26 N8 O . 2HCl; Mol wt: 491.4242

ACTION – Agent for the treatment of migraine and venous insufficiency that is reported to possess high selectivity for 5-HT_{1B}, 5-HT_{1D} or 5-HT₁-like receptors. It induces contractions of rabbit saphenous vein with an EC₅₀ value of 0.12 μM (concentration required to produce 50% of the maximum contraction elicited by KCl). Other specifically claimed indole and indazole derivatives include the following:



Compound	R1	A	X	Formula
274397	N(Et)2	CH	2HCl	C ₁₆ H ₂₁ N ₅ ·2HCl
274398	N(Et)2	N	2HCl	C ₁₅ H ₂₀ N ₆ ·2HCl
274399	4-(5-MeO-4-pyrimidinyl)-1-Piz-CH2	N		C ₂₁ H ₂₅ N ₉ O

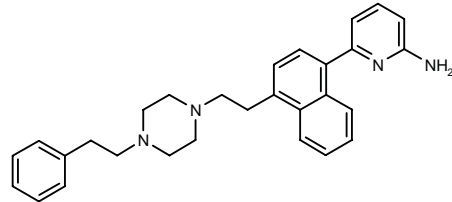
SOURCE – ADIR.

REFERENCES

1. Lavielle, G. et al. (ADIR et Cie.) *Indole and indazole derivs., process for their preparation and the pharmaceutical compsns. containing them.* EP 902027.

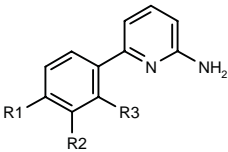
274520

6-[4-[2-[4-(2-Phenylethyl)-1-piperazinyl]ethyl]-1-naphthalenyl]-2-pyridinylamine



C29 H32 N4; Mol wt: 436.5998

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment or prevention of migraine, septic shock, inflammation, stroke, inflammatory bowel disease, neurodegenerative diseases, rheumatoid arthritis, adult respiratory distress syndrome and cancer. A representative compound from a series of 2-aminopyridine derivatives, wherein the following are also included:



Compound	R1	R2,R3	Formula
274521	2-furyl-CH2NHCH2CH2	-CH=CHCH=CH-	C ₂₂ H ₂₁ N ₃ O
274524	4-morpholinyl-CH2CH2O	-CH=CHCH=CH-	C ₂₁ H ₂₃ N ₃ O ₂
274525	1-(2-furyl-CH2)-4-Pip-O	-CH=CHCH=CH-	C ₂₅ H ₂₅ N ₃ O ₂
274526	OCH2CH2N(i-Pr)2	-(CH2)4-	C ₂₃ H ₃₃ N ₃ O
274527	1-i-Bu-3-Pip-CH2O	-(CH2)4-	C ₂₅ H ₃₅ N ₃ O
274529	OCH2CH2N(Me)CH2Ph	-(CH2)3-	C ₂₄ H ₂₇ N ₃ O
274531	2-NH2-cyclohexyl-O	-(CH2)4-	C ₂₁ H ₂₇ N ₃ O

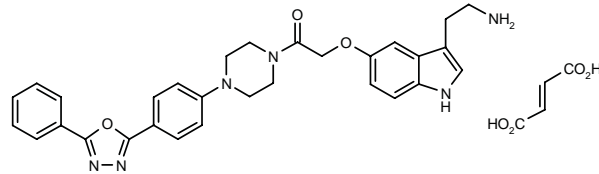
SOURCE – Pfizer.

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1. Lowe, J.A. III (Pfizer Products Inc.) *2-Aminopyridines containing fused ring substituents as NOS inhibitors.* WO 9910339.

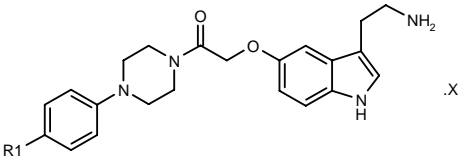
274733

2-[3-(2-Aminoethyl)-1*H*-indol-5-yloxy]-1-[4-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-1-piperazinyl]-1-ethanone fumarate



C30 H30 N6 O3 . C4 H4 O4; Mol wt: 638.6776

ACTION – Agent for the treatment of migraine and vasospastic disorders, as well as CNS disorders including depression, anxiety and neurodegenerative disorders such as Alzheimer's disease, that acts as a potent and selective agonist at human 5-HT_{1B} and 5-HT_{1D} receptors. Other exemplified indole derivatives include the following:



Compound	R1	X	Formula
274734	5-(2-Me-Ph)-1,3,4-oxadiazol-2-yl	fumarate	C ₃₁ H ₃₂ N ₆ O ₃ ·C ₄ H ₄ O ₄
274735	5-(4-Me-Ph)-1,3,4-oxadiazol-2-yl	fumarate	C ₃₁ H ₃₂ N ₆ O ₃ ·C ₄ H ₄ O ₄
274736	5-Me-1,3,4-oxadiazol-2-yl	fumarate	C ₂₅ H ₂₈ N ₆ O ₃ ·C ₄ H ₄ O ₄
274737	4,5-dihydro-2-oxazolyl	fumarate	C ₂₅ H ₂₉ N ₅ O ₃ ·C ₄ H ₄ O ₄
274738	2-oxazolyl	2HCl	C ₂₅ H ₂₇ N ₅ O ₃ ·2HCl
274739	2-benzothiazolyl	fumarate	C ₂₉ H ₂₉ N ₅ O ₂ S·C ₄ H ₄ O ₄
274740	2H-tetrazol-5-yl	HCl	C ₂₃ H ₂₆ N ₆ O ₂ ·HCl
274741	4-Pyr	fumarate	C ₂₇ H ₂₉ N ₅ O ₂ ·C ₄ H ₄ O ₄
274742	2-thienyl	fumarate	C ₂₆ H ₂₈ N ₄ O ₂ S·C ₄ H ₄ O ₄
274743	3-thienyl	fumarate	C ₂₆ H ₂₈ N ₄ O ₂ S·C ₄ H ₄ O ₄

SOURCE – Pierre Fabre.

REFERENCES

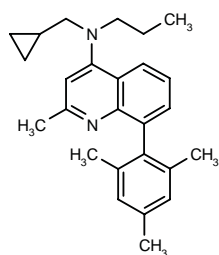
1. Perez, M. and Halazy, S. (Pierre Fabre Médicament) *Indole derivs. as 5-HT_{1B} and 5-HT_{1D} agonists*. WO 9910344.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

273688

N-(Cyclopropylmethyl)-*N*-[2-methyl-8-(2,4,6-trimethylphenyl)quinolin-4-yl]-*N*-propylamine



C26 H32 N2; Mol wt: 372.5528

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist ($K_i = 0.3$ nM), potentially useful for the treatment of stress-related disorders such as anxiety and depression.

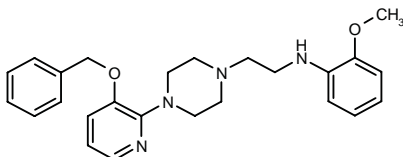
SOURCES – Janssen; Neurocrine Biosciences.

REFERENCES

1. Huang, C. et al. (Janssen Pharmaceutica NV; Neurocrine Biosciences, Inc.) *CRF antagonistic quino- and quinazolines*. WO 9847874.
2. Huang, C.Q. et al. *Design, synthesis and structure activity relationship (SAR) of 8-arylquinoline corticotropin releasing factor 1 (CRF1) receptor antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 003.

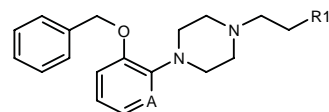
273737

N-[2-[4-[3-(Benzyloxy)-2-pyridinyl]-1-piperazinyl]ethyl]-*N*-(2-methoxyphenyl)amine



C25 H30 N4 O2; Mol wt: 418.5380

ACTION – Anxiolytic agent, a potent 5-HT₂ receptor antagonist ($IC_{50} = 1.5$ nM) and 5-HT_{1A} receptor agonist ($IC_{50} = 0.5$ nM). It demonstrated anxiolytic activity in a rat model at 10 mg/kg p.o. and was shown to inhibit DOI-induced head twitching with an ED_{50} value of 6.5 mg/kg p.o. Other compounds from this series of substituted piperazine derivatives include the following:



Compound	R1	A	Formula
273738	4-F-PhNHCH2CH2	CH	C ₂₇ H ₃₂ FN ₃ O
273739	2-I-PhNH	CH	C ₂₅ H ₂₆ IN ₃ O
273740	3-Me-PhNHCH2CH2	N	C ₂₇ H ₃₄ N ₄ O
273741	4-Me-PhNH	CH	C ₂₆ H ₃₁ N ₃ O
273742	4-Me-PhNHCH2CH2	N	C ₂₇ H ₃₄ N ₄ O
273743	2-Et-PhNH	CH	C ₂₇ H ₃₃ N ₃ O
273744	4-Et-PhNH	CH	C ₂₇ H ₃₃ N ₃ O
273745	4-Pr-PhNHCH2CH2	CH	C ₃₀ H ₃₉ N ₃ O

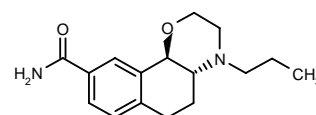
SOURCE – Sankyo.

REFERENCES

1. Naruto, S. et al. (Sankyo Co., Ltd.) *Piperazine derivs*. JP 99080119, WO 9903833.

273930

(+)-*trans*-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-*b*][1,4]oxazine-9-carboxamide



C16 H22 N2 O2; Mol wt: 274.3618

ACTION – Agent for the treatment of anxiety, depression, Parkinson's disease and schizophrenia that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors ($pK_i = 8$ and 6.5, respectively). *In vivo*, compound exhibited anxiolytic activity, as demonstrated by a significant reduction in the duration of ultrasonic vocalization in rats at 0.04 and 0.16 mg/kg s.c. Compound also demonstrated potent antidepressant activity in the forced swimming test in rats ($ID_{50} = 0.41$ mg/kg s.c.). In addition, compound was shown to increase contralateral turning in rats with unilateral 6-OHDA lesions of the substantia nigra at 0.04 mg/kg s.c. A specifically claimed compound from a series of 3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-*b*][1,4]oxazines.

SOURCE – ADIR.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) *Disubstd. trans-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b]-1,4-oxazines, process for their preparation and pharmaceutical compsns. containing them*. EP 899267.

SOURCE – Pierre Fabre.

REFERENCES

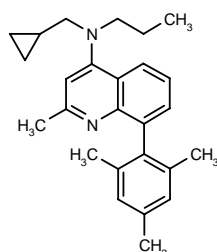
1. Perez, M. and Halazy, S. (Pierre Fabre Médicament) *Indole derivs. as 5-HT_{1B} and 5-HT_{1D} agonists*. WO 9910344.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

273688

N-(Cyclopropylmethyl)-*N*-[2-methyl-8-(2,4,6-trimethylphenyl)quinolin-4-yl]-*N*-propylamine



C26 H32 N2; Mol wt: 372.5528

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist ($K_i = 0.3$ nM), potentially useful for the treatment of stress-related disorders such as anxiety and depression.

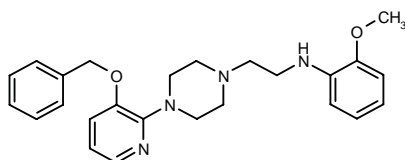
SOURCES – Janssen; Neurocrine Biosciences.

REFERENCES

1. Huang, C. et al. (Janssen Pharmaceutica NV; Neurocrine Biosciences, Inc.) *CRF antagonistic quino- and quinazolines*. WO 9847874.
2. Huang, C.Q. et al. *Design, synthesis and structure activity relationship (SAR) of 8-arylquinoline corticotropin releasing factor 1 (CRF1) receptor antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 003.

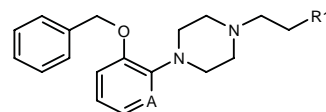
273737

N-[2-[4-[3-(Benzyloxy)-2-pyridinyl]-1-piperazinyl]ethyl]-*N*-(2-methoxyphenyl)amine



C25 H30 N4 O2; Mol wt: 418.5380

ACTION – Anxiolytic agent, a potent 5-HT₂ receptor antagonist ($IC_{50} = 1.5$ nM) and 5-HT_{1A} receptor agonist ($IC_{50} = 0.5$ nM). It demonstrated anxiolytic activity in a rat model at 10 mg/kg p.o. and was shown to inhibit DOI-induced head twitching with an ED_{50} value of 6.5 mg/kg p.o. Other compounds from this series of substituted piperazine derivatives include the following:



Compound	R1	A	Formula
273738	4-F-PhNHCH2CH2	CH	C ₂₇ H ₃₂ N ₃ O
273739	2-I-PhNH	CH	C ₂₅ H ₂₆ N ₃ O
273740	3-Me-PhNHCH2CH2	N	C ₂₇ H ₃₄ N ₄ O
273741	4-Me-PhNH	CH	C ₂₆ H ₃₁ N ₃ O
273742	4-Me-PhNHCH2CH2	N	C ₂₇ H ₃₄ N ₄ O
273743	2-Et-PhNH	CH	C ₂₇ H ₃₃ N ₃ O
273744	4-Et-PhNH	CH	C ₂₇ H ₃₃ N ₃ O
273745	4-Pr-PhNHCH2CH2	CH	C ₃₀ H ₃₉ N ₃ O

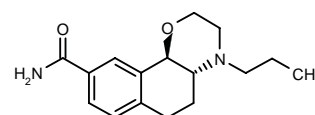
SOURCE – Sankyo.

REFERENCES

1. Naruto, S. et al. (Sankyo Co., Ltd.) *Piperazine derivs*. JP 99080119, WO 9903833.

273930

(+)-*trans*-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-*b*][1,4]oxazine-9-carboxamide



C16 H22 N2 O2; Mol wt: 274.3618

ACTION – Agent for the treatment of anxiety, depression, Parkinson's disease and schizophrenia that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors ($pK_i = 8$ and 6.5, respectively). *In vivo*, compound exhibited anxiolytic activity, as demonstrated by a significant reduction in the duration of ultrasonic vocalization in rats at 0.04 and 0.16 mg/kg s.c. Compound also demonstrated potent antidepressant activity in the forced swimming test in rats ($ID_{50} = 0.41$ mg/kg s.c.). In addition, compound was shown to increase contralateral turning in rats with unilateral 6-OHDA lesions of the substantia nigra at 0.04 mg/kg s.c. A specifically claimed compound from a series of 3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-*b*][1,4]oxazines.

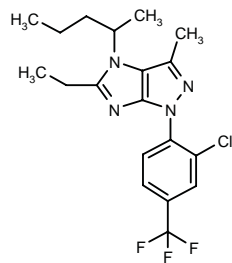
SOURCE – ADIR.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) *Disubstd. trans-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b]-1,4-oxazines, process for their preparation and pharmaceutical compsns. containing them*. EP 899267.

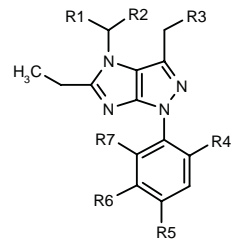
274825

1-[2-Chloro-4-(trifluoromethyl)phenyl]-5-ethyl-3-methyl-4-(1-methylbutyl)-1,4-dihydroimidazo[4,5-c]pyrazole



C19 H22 Cl F3 N4; Mol wt: 398.8578

ACTION – Agent for the treatment of psychiatric and neurological disorders such as anxiety and depression, a corticotropin-releasing factor (CRF) antagonist. Within this series of nitrogen-substituted imidazo[4,5-c]pyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
274827	Me	Pr	F	Cl	Cl	H	Cl	C ₁₈ H ₂₀ Cl ₃ FN ₄
274828	Pr	Et	H	Cl	Br	H	Cl	C ₁₉ H ₂₃ BrCl ₂ N ₄
274829	Pr	Et	H	Cl	Cl	Cl	H	C ₁₉ H ₂₃ Cl ₃ N ₄
274830	Pr	Et	H	Br	i-Pr	H	H	C ₂₂ H ₃₁ BrN ₄
274831	H	Pr	H	Cl	Br	H	Cl	C ₁₇ H ₁₉ BrCl ₂ N ₄
274832	H	Ph	H	Cl	Br	H	Cl	C ₂₀ H ₁₇ BrCl ₂ N ₄

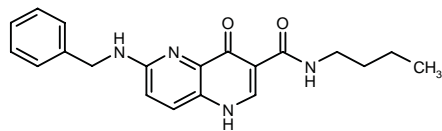
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Beck, J.P. and Gilligan, P.J. (DuPont Pharmaceuticals Co.) *Nitrogen subst. imidazo[4,5-c]pyrazoles as corticotropin relasing hormone antagonists*. WO 9910350.

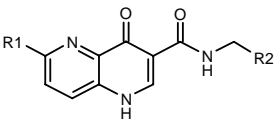
274840

6-Benzylamino-*N*-butyl-4-oxo-1,4-dihydro[1,5]naphthyridine-3-carboxamide



C20 H22 N4 O2; Mol wt: 350.4198

ACTION – Agent for the treatment of anxiety, overdose with benzodiazepine-type drugs, Down’s syndrome, and sleep, seizure and cognitive disorders with affinity for brain GABA_A receptors and which acts as an agonist, inverse agonist or antagonist at these receptors. Within this series of specifically claimed substituted 4-oxo-naphthyridine-carboxamide derivatives, the following are also included:



Compound	R1	R2	Formula
274841	OMe	CH2SEt	C ₁₄ H ₁₇ N ₃ O ₃ S
274842	OEt	i-Bu	C ₁₆ H ₂₁ N ₃ O ₃
274843	OMe	3-F-Ph	C ₁₇ H ₁₄ FN ₃ O ₃
274844	OEt	4-MeO-Ph	C ₁₉ H ₁₉ N ₃ O ₄
274845	4-morpholinyl	i-Bu	C ₁₈ H ₂₄ N ₄ O ₃
274846	OEt	4-(MeNHCH2)-Ph	C ₂₀ H ₂₂ N ₄ O ₃
274847	N(Me)2	4-[MeNHCH(Me)]-Ph	C ₂₁ H ₂₅ N ₅ O ₂
274848	OCH2CH2NHMe	Ph	C ₁₉ H ₂₀ N ₄ O ₃

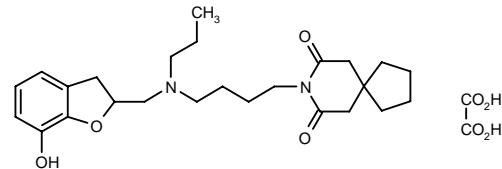
SOURCE – Neurogen.

REFERENCES

1. Albaugh, P. et al. (Neurogen Corp.) *Subst. 4-oxo-naphthyridine-3-carboxamides as GABA brain receptor ligands*. WO 9910347.

274875

8-[4-[*N*-(7-Hydroxy-2,3-dihydro-1-benzofuran-2-yl)methyl]-*N*-propylaminobutyl]-8-azaspiro[4.5]decane-7,9-dione oxalate



C25 H36 N2 O4 . C2 H2 O4; Mol wt: 518.6032

Yellow solid.

ACTION – High-affinity ligand for 5-HT_{1A} receptors (IC₅₀ = 1.5 nM against [³H]-8-OH-DPAT binding in rat hippocampus membranes) with high selectivity (> 100-fold) over 5-HT_{2A}, 5-HT_{2C}, 5-HT₃ and dopamine D₂ receptors. Potentially useful for elucidating the pathophysiological role of 5-HT_{1A} receptors, as well as being a promising candidate for future development in the treatment of anxiety and/or depression.

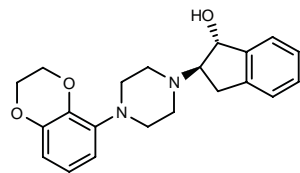
SOURCE – Servier.

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1. Boyé, S. et al. *N,N*-Disubstituted aminomethyl benzofuran derivatives: *Synthesis and preliminary binding evaluation*. Bioorg Med Chem 1999, 7(2): 335.

275000

trans-2-[4-(2,3-Dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]indan-1-ol



C21 H24 N2 O3; Mol wt: 352.4316

ACTION – Agent for the treatment of CNS disorders and pain that exhibits high affinity and selectivity for 5-HT_{1A} receptors ($K_i = 1.73$ nM) relative to α_1 -adrenoceptors ($K_i = 932$ nM). *In vivo*, compound behaved as a presynaptic 5-HT_{1A} receptor agonist, as demonstrated by its ability to decrease the frequency of neuronal discharge in anesthetized rats ($ID_{50} = 0.59$ μ g/kg i.v.), whereas it behaved as a 5-HT_{1A} receptor antagonist at the postsynaptic level, as demonstrated by its ability to reverse 8-OH-DPAT-induced hypothermia in rats ($ID_{50} = 1.3$ mg/kg s.c.). Anxiolytic activity was demonstrated in rats by a significant reduction in the duration of ultrasonic vocalization at 0.16 and 2.5 mg/kg s.c. A representative compound from a series of indanol derivatives.

SOURCE – ADIR.

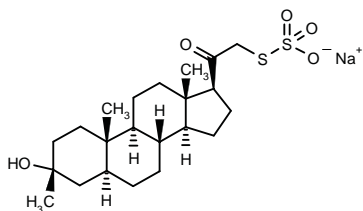
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CO-122739

273902

3 α -Hydroxy-3-methyl-21-(sulfosulfanyl)-5 α -pregnan-20-one sodium salt



C22 H35 Na O5 S2; Mol wt: 466.6355

ACTION – Allosteric GABA_A receptor modulator, a neuroactive steroid derivative with an IC_{50} value of 151 nM for inhibition of [³⁵S]-TBPS binding. *In vivo*, compound showed anticonvulsant activity against pentylenetetrazol-induced seizures in mice (62.5 and 75% protection at 20 mg/kg i.p. and 40 mg/kg p.o., respectively). Compound also showed anxiolytic activity in a conflict test in rats, with a minimum effective dose of 5.7 mg/kg p.o.

SOURCE – CoCensys.

REFERENCES

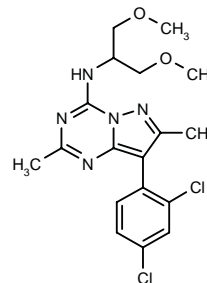
1. Upasani, R.B. et al. (CoCensys, Inc.) *Androstanes and pregnanes for allosteric modulation of GABA receptor*. EP 752860, JP 97510701, WO 9521617.
2. Fick, D.B. et al. *Sodium S-(3 α -hydroxypregnan-20-on-21-yl)thiosulfates: Allosteric modulators of the GABA_A receptor*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 098.

DMP-696

273689

8-(2,4-Dichlorophenyl)-N-[2-methoxy-1-(methoxymethyl)-ethyl]-2,7-dimethylpyrazolo[1,5-a][1,3,5]triazin-4-amine

SK-696



C18 H21 Cl2 N5 O2; Mol wt: 410.3029

ACTION – Potent corticotropin-releasing factor (CRF) receptor antagonist ($K_i = 1.7$ nM) with high functional inhibitory activity against CRF-stimulated adenylate cyclase activity ($IC_{80} = 82$ nM). Compound exhibited excellent oral bioavailability in rats, dogs and rhesus monkeys, and good anxiolytic activity in rat and primate models. Potentially useful in the treatment of anxiety, depression and other psychiatric disorders, as well as immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbances and stress.

SOURCE – DuPont Pharmaceuticals.

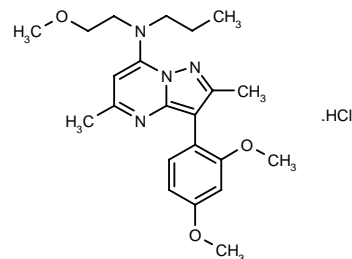
REFERENCES

1. Arvanitis, A.G. and Chorvat, R.J. (The Du Pont Merck Pharmaceutical Co.) *Azolo triazines and pyrimidines*. WO 9803510.
2. He, L. et al. *DMP696: A potent, orally bioavailable pyrazolo-[1,5-a]-s-triazine corticotropin releasing factor (CRF) antagonist*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 004.
3. He, L. et al. *Pyrazolo-[1,5-a]-s-triazines as novel hCRF1 receptor antagonists: Design, synthesis and structure activity relationships*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 107.

NBI-30545

273687

N-[3-(2,4-Dimethoxyphenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-methoxyethyl)-N-propylamine hydrochloride



C22 H30 N4 O3 . HCl; Mol wt: 434.9649

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist ($K_i = 2.8$ nM) with anxiolytic activity in rats and excellent oral bioavailability in mice (80%), but not in rats (10%). Potentially useful for the treatment of depression and anxiety-related disorders.

SOURCES – Janssen; Neurocrine Biosciences.

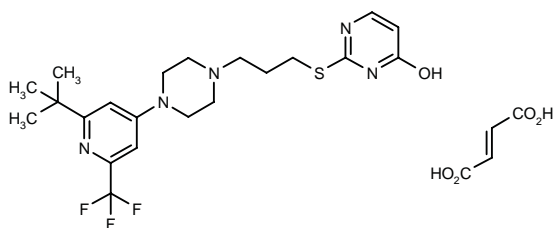
REFERENCES

- Chen, C. et al. (Janssen Pharmaceutica NV; Neurocrine Biosciences Inc.) *Pyrazolopyrimidines as CRF receptor antagonists*. EP 880523, WO 9729109.
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ANTIPSYCHOTIC DRUGS

274024

2-[3-[4-[2-*tert*-Butyl-6-(trifluoromethyl)-4-pyridinyl]-1-piperazinyl]propylsulfanyl]pyrimidin-4-ol fumarate



C₂₁ H₂₈ F₃ N₅ O₄ S . C₄ H₄ O₄; Mol wt: 571.6178

ACTION – Novel fumarate salt of a known dopamine D₃ receptor antagonist reported to possess improved water solubility compared to the free base and thus expected to be more suitable for oral or parenteral administration. Potentially useful particularly for the treatment of schizophrenia.

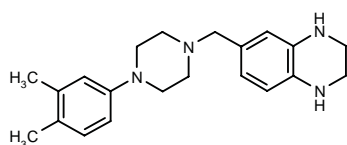
SOURCE – BASF.

REFERENCES

- Blank, S. et al. (BASF AG) *2-[3-[4-(2-*t*-Butyl-6-trifluoromethylpyridin-4-yl)piperazin-1-yl]propylmercapto]pyrimidin-4-ol-fumarate*. WO 9909015.

274473

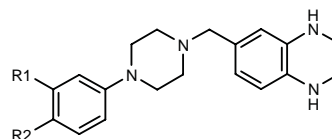
6-[4-(3,4-Dimethylphenyl)-1-piperazinylmethyl]-1,2,3,4-tetrahydroquinoxaline



C₂₁ H₂₈ N₄; Mol wt: 336.4802

ACTION – Potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding assays by K_i values of 2.8 and 2941 nM for D₄ and D₂ receptors, respectively. *In vitro*, compound was also shown to inhibit [³H]-thymidine uptake in CHO cells transfected with the

human D₄ receptor with an IC₅₀ value of 1.6 nM. *In vivo*, it was shown to increase dopamine synthesis in the hippocampus and striatum in rats following i.p. administration. Potentially useful for the treatment of psychosis and schizophrenia. Other compounds from this series of tetrahydroquinoxaline derivatives include the following:



Compound	R1	R2	Formula
274475	Cl	Me	C ₂₀ H ₂₅ ClN ₄
274476	Cl	Cl	C ₁₉ H ₂₂ Cl ₂ N ₄

SOURCE – Warner-Lambert.

REFERENCES

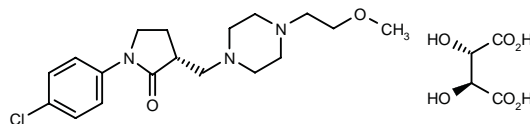
- Glase, S.A. and Kesten, S.R. (Warner-Lambert Co.) *Tetrahydroquinoxaline dopamine D₄ receptor antagonists*. US 5885994.

MS-377*

273886

265151 (as dihydrochloride)

1-(4-Chlorophenyl)-3(*R*)-[4-(2-methoxyethyl)-1-piperazinylmethyl]pyrrolidin-2-one (–)-D-tartrate



C₁₈ H₂₆ Cl N₃ O₂ . C₄ H₆ O₆; Mol wt: 501.9608

ACTION – Antipsychotic agent, a high-affinity σ_1 -receptor antagonist. Compound (3 mg/kg p.o.) enhanced the efficacy of the dopamine D₂ receptor antagonist haloperidol in suppressing climbing behavior in mice, which appeared to be due to indirect inhibition of dopamine neurons via the σ_1 -receptor. No extrapyramidal effects are associated with the compound since it has no affinity for dopamine receptors. Potentially useful in the treatment of CNS disorders such as schizophrenia, dementia, manic-depressive psychosis and anxiety.

SOURCE – Mitsui Pharmaceuticals.

REFERENCES

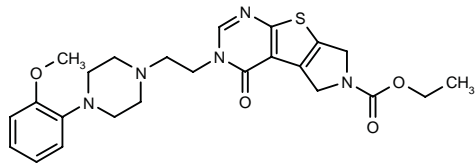
- Mita, N. et al. (Mitsui Chemicals, Inc.) *Pyrrolidinone derivs. and their use as antipsychotic medicaments*. EP 839805, JP 98182602.
- Takagi, K. et al. *Involvement in sigma receptor on the enhanced efficacy of haloperidol in combination with MS-377, a novel antipsychotic agent*. Jpn J Pharmacol 1999, 79(Suppl. 1): Abst P-492.

*Identified compound **265151** Drug Data Report 1998, 020(08): 0661.

ANTIDEPRESSANTS

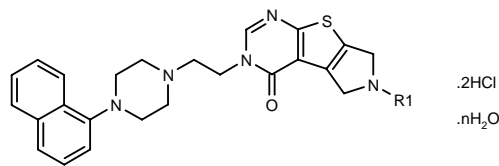
273854

3-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-4-oxo-3,4,6,7-tetrahydro-5H-pyrrolo[3',4':4,5]thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

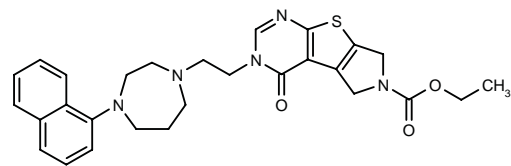


C24 H29 N5 O4 S; Mol wt: 483.5901

ACTION – Antidepressant, a 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist and 5-HT reuptake inhibitor. Other exemplified compounds from this series of 3,4,6,7-tetrahydro-5H-pyrrolo[3',4':4,5]thieno[2,3-d]pyrimidine derivatives include the following:



Compound	R1	n	Formula
273857	H	2	C ₂₄ H ₂₅ N ₅ OS.2HCl.2H ₂ O
273858	Et	3	C ₂₆ H ₂₉ N ₅ OS.2HCl.3H ₂ O



273855: C28 H31 N5 O3 S

SOURCE – BASF.

REFERENCES

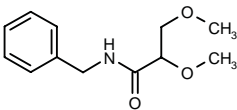
1. Steiner, G. et al. (BASF AG) 3-Substd. 3,4,5,7-tetrahydro-pyrrolo 3',4':4,5 thieno 2,3-d pyrimidine derivs., their preparation and use as 5HT antagonists. WO 9907711.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

273951

N-Benzyl-2,3-dimethoxypropionamide



C12 H17 N O3; Mol wt: 223.2703

ACTION – Anticonvulsant whose activity was demonstrated in the maximal electroshock seizure (MES) model in mice (ED₅₀ = 30 mg/kg i.p.); the median toxic dose (TD₅₀) was determined in the rotarod test to be 280 mg/kg i.p. and the compound thus exhibits a good protective index (TD₅₀/ED₅₀ = 9.3).

SOURCE – Research Corporation Technologies.

REFERENCES

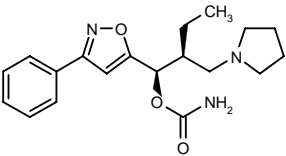
1. Kohn, H. (Research Corporation Technologies, Inc.) *Propionamide anticonvulsants*. US 5880158.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

MR-2917

274120

Carbamic acid 1(R)-(3-phenyl-5-isoxazolyl)-2(S)-(1-pyrrolidinylmethyl)butyl ester



C19 H25 N3 O3; Mol wt: 343.4245

ACTION – Central muscle relaxant.

SOURCE – Maruho.

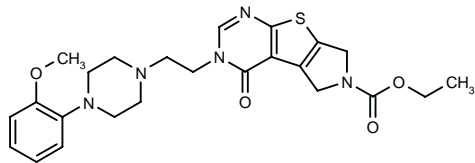
REFERENCES

1. Tanaka, Y. et al. *Novel central muscle relaxant (1) - Synthesis of novel muscle relaxant (MR-2917) having carbamoyloxy group*. 119th Annu Meet Pharm Soc Jpn (March 29-31, Tokushima) 1999, Abst 29(PO)10-075.

ANTIDEPRESSANTS

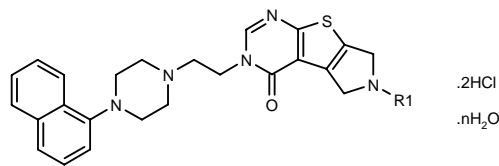
273854

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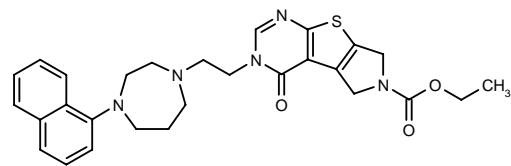


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Compound	R1	n	Formula
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273858	Et	3	C ₂₆ H ₂₉ N ₅ OS.2HCl.3H ₂ O



273855: C28 H31 N5 O3 S

SOURCE – BASF.

REFERENCES

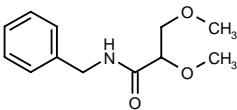
1. Steiner, G. et al. (BASF AG) 3-Substd. 3,4,5,7-tetrahydro-pyrrolo 3',4':4,5 thieno 2,3-d pyrimidine derivs., their preparation and use as 5HT antagonists. WO 9907711.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

273951

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SOURCE – Research Corporation Technologies.

REFERENCES

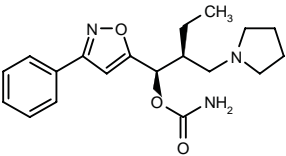
1. Kohn, H. (Research Corporation Technologies, Inc.) *Propionamide anticonvulsants*. US 5880158.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

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C19 H25 N3 O3; Mol wt: 343.4245

ACTION – Central muscle relaxant.

SOURCE – Maruho.

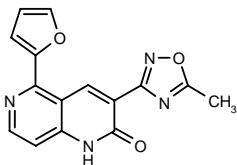
REFERENCES

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COGNITION-ENHANCING DRUGS

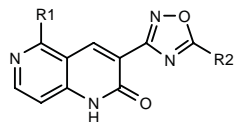
273254

5-(2-Furyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1,6-naphthyridin-2(1H)-one

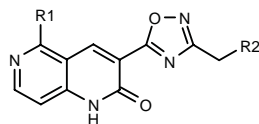


C15 H10 N4 O3; Mol wt: 294.2690

ACTION – Agent for the treatment of cognitive disorders such as Alzheimer’s disease, a potent GABA_A receptor benzodiazepine binding site ligand (IC₅₀ = 0.61 nM against [³H]-diazepam binding in rat brain synaptosome preparations) proven to behave as an inverse agonist in a TBPS binding assay in rat cortex preparations. A representative compound from a series of substituted 1,6-naphthyridin-2(1H)-one derivatives, wherein the following are also included:



Compound	R1	R2	Formula
273255	cyclopropyl	Et	C ₁₅ H ₁₄ N ₄ O ₂
273256	3-F-Ph	Et	C ₁₈ H ₁₃ FN ₄ O ₂
273257	Ph	i-Pr	C ₁₉ H ₁₆ N ₄ O ₂
273258	Ph	cyclopropyl	C ₁₉ H ₁₄ N ₄ O ₂
273259	2-furyl	Et	C ₁₆ H ₁₂ N ₄ O ₃
273260	2-thienyl	Et	C ₁₆ H ₁₂ N ₄ O ₂ S
273261	2-furyl	cyclopropyl	C ₁₇ H ₁₂ N ₄ O ₃
273262	2-thienyl	cyclopropyl	C ₁₇ H ₁₂ N ₄ O ₂ S



Compound	R1	R2	Formula
273263	2-thienyl	H	C ₁₅ H ₁₀ N ₄ O ₂ S
273264	3-F-Ph	Me	C ₁₈ H ₁₃ FN ₄ O ₂
273265	2-furyl	Me	C ₁₆ H ₁₂ N ₄ O ₃
273266	2-furyl	Et	C ₁₇ H ₁₄ N ₄ O ₃

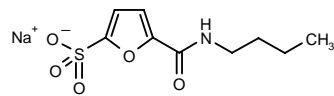
SOURCE – Dainippon Pharmaceutical.

REFERENCES

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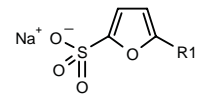
274032

5-(Butylcarbamoyl)furan-2-sulfonic acid sodium salt



C9 H12 N Na O5 S; Mol wt: 269.2518

ACTION – Agent for the treatment of neurodegenerative disorders such as Alzheimer’s disease that acts by inhibiting the formation of Aβ(1-40) β-pleated sheets and inhibits the release of cytokines such as IL-1β, IL-6 and tumor necrosis factor (TNF-α). Compound provided at least 60% protection against neuronal cell loss induced by Aβ(25-35) in rat embryonic hippocampal cell cultures at a concentration of 100 μM. *In vivo*, it reduced the locomotor impairment caused by Aβ(25-35) and reduced the cognitive deficits that develop in certain strains of autoimmune mice. Within this series of furansulfonic acid derivatives, the following are also included.



Compound	R1	Formula
274035	i-PrNHCO	C ₉ H ₁₀ NNaO ₅ S
274036	-CH=CHCONHBu	C ₁₁ H ₁₄ NNaO ₅ S
274037	CH2CH2CONHBu	C ₁₁ H ₁₆ NNaO ₅ S

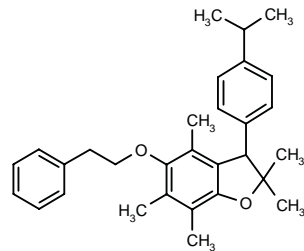
SOURCE – Centaur.

REFERENCES

1. Kelleher, J.A. et al. (Centaur Pharmaceuticals, Inc.) Furansulfonic acid derivs. and pharmaceutical compsns. containing the same. WO 9909022.

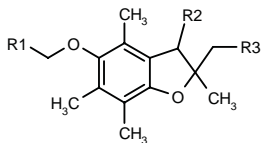
275086

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(2-phenylethoxy)-2,3-dihydro-1-benzofuran



C30 H36 O2; Mol wt: 428.6124

ACTION – Agent for the treatment of Alzheimer’s disease found to protect human neuroblastoma SK-N-SH cells from β-amyloid toxicity in an *in vitro* assay. Within this series of heterocyclic compounds, the following are also included:



Compound	R1	R2	R3	Formula
275087	Ph	4-i-Pr-Ph	H	C ₂₉ H ₃₄ O ₂
275088	Ph	4-N(Me)2-Ph	H	C ₂₈ H ₃₃ NO ₂
275089	Ph	H	4-Ph-1-Pip	C ₃₁ H ₃₇ NO ₂
275090	4-MeO-Ph	4-i-Pr-Ph	H	C ₃₀ H ₃₆ O ₃
275091	4-MeO-Ph	4-(4-morpholinyl)-Ph	H	C ₃₁ H ₃₇ NO ₄
275092	(E)-CH=CHPh	4-i-Pr-Ph	H	C ₃₁ H ₃₆ O ₂
275093	CH2CH(Ph)2	4-i-Pr-Ph	H	C ₃₇ H ₄₂ O ₂

SOURCE – Takeda.

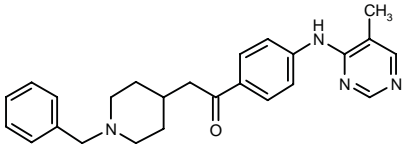
REFERENCES

1. Ohkawa, S. et al. (Takeda Chemical Industries, Ltd.) *Heterocyclic cpds., their preparation method and agents*. JP 99049765.

UR-1827*

230177

2-(1-Benzylpiperidin-4-yl)-1-[4-(5-methylpyrimidin-4-ylamino)phenyl]-1-ethanone



C25 H28 N4 O; Mol wt: 400.5280

ACTION – Acetylcholinesterase (AChE) inhibitor (IC₅₀ = 0.25 μM) with additional inhibitory activity against monoamine oxidase A (MAO-A) and norepinephrine reuptake (IC₅₀ = 0.34 and 0.064 μM, respectively). *Ex vivo* studies in rodents showed that compound given orally inhibited cerebral AChE and MAO-A levels (ED₅₀ = 16.4 and 16.0 mg/kg in mice and 31.0 and 23.8 mg/kg in rats, respectively). Compound (25-100 mg/kg p.o.) increased brain ACh, dopamine and 3-MT and decreased DOPAC, HVA and 5-HIAA levels in microdialysis studies. It was active in rat cholinergic dysfunction models, reversing both scopolamine-induced high-voltage slow waves in cortical EEG and memory impairment in a passive avoidance task at doses of 30 and 10 mg/kg i.p., respectively. UR-1827 ameliorated monoaminergic deficiency, antagonizing reserpine-induced apoptosis (ED₅₀ = 7.4 and 35.2 mg/kg p.o. in rats and mice, respectively), and potentiated L-DOPA-induced rapid running in mice (ED₅₀ = 16.1 mg/kg p.o.). Moreover, the compound (30 mg/kg i.p.) showed antidepressant-like activity, reducing the duration of immobility in the forced swimming test in mice. Potentially useful for the treatment of cognitive dysfunction and depressive syndrome in Alzheimer's disease.

SOURCE – Ube.

REFERENCES

1. Kimura, T. et al. (Ube Industries, Ltd.) *Pyrimidine cpd*. EP 664291, WO 9407890.

2. Anpeiji, S. et al. *Pharmacological profiles of UR-1827, a novel acetylcholinesterase inhibitor with inhibitory activities on both monoamine oxidase A and NE uptake*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-463.

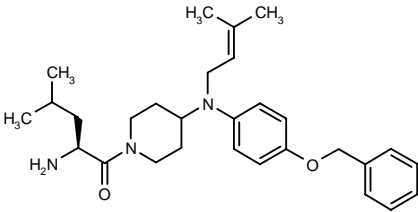
3. Fujiwara, H. et al. *Neurochemical profiles of UR-1827, a novel acetylcholinesterase inhibitor with inhibitory activities on both monoamine oxidase A and NE uptake*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-418.

*Identified compound **230177** (see **228237**) Drug Data Report 1996, 018(02): 0123.

TREATMENT OF
CEREBROVASCULAR DISEASES

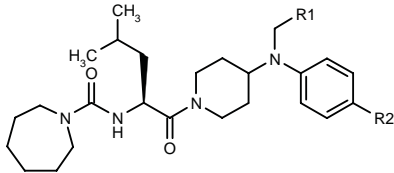
273647

2-(S)-Amino-1-[4-[N-(4-benzyloxyphenyl)-N-(3-methyl-2-butenyl)amino]-1-piperidinyl]-4-methyl-1-pentanone

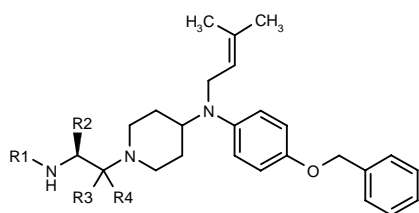


C29 H41 N3 O2; Mol wt: 463.6619

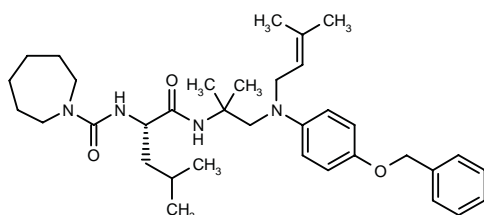
ACTION – N-type calcium channel blocker, as demonstrated *in vitro* by inhibition of Ca²⁺ influx in IMR-32 cells (IC₅₀ = 2.4 μM). *In vivo*, it completely (100%) protected mice against high-frequency sound signal-induced seizures at 10 mg/kg i.v. Potentially useful for the treatment of stroke, cerebral ischemia, pain, head trauma and epilepsy. Other compounds from this series of aniline derivatives include the following:



Compound	R1	R2	Formula
273649	CH=C(Me)2	OCH2Ph	C ₃₆ H ₅₂ N ₄ O ₃
273652	CH=C(Me)2	OCH2Ph	C ₃₆ H ₅₂ N ₄ O ₃
273653	CH=C(Me)2	NHCO2CH2Ph	C ₃₇ H ₅₃ N ₅ O ₄
273654	i-Bu	t-BuCH2CH2NH	C ₃₅ H ₆₁ N ₅ O ₂
273655	i-Bu	cyclohexyl-CH2NH	C ₃₆ H ₆₁ N ₅ O ₂



Compound	R1	R2	R3	R4	Formula
273650	H	CH(Me)Et	-O-		C ₂₉ H ₄₁ N ₃ O ₂
273651	2-pyrrolyl-CH ₂	i-Bu	-O-		C ₃₄ H ₄₆ N ₄ O ₂
273656	H	i-Bu	H	H	C ₂₉ H ₄₃ N ₃ O



273648: C₃₅ H₅₂ N₄ O₃

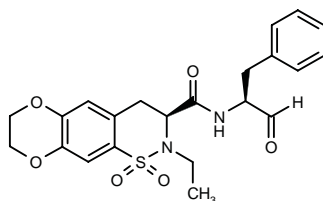
SOURCE – Warner-Lambert.

REFERENCES

- Hu, L.-Y. et al. (Warner-Lambert Co.) *Aniline derivs. as calcium channel blockers*. WO 9907689.

273747

2-Ethyl-*N*-[1-formyl-2(*S*)-phenylethyl]-1,1-dioxo-1,2,3,4,7,8-hexahydro-1,4-dioxino[2,3-*g*]-1,2-benzothiazine-3(*S*)-carboxamide



C₂₂ H₂₄ N₂ O₆ S; Mol wt: 444.5056

ACTION – Inhibitor of the cysteine protease calpain I (IC₅₀ = 7 nM) with submicromolar activity in a MOLT-4 whole-cell assay (IC₅₀ = 0.5 μM). *In vivo* in a gerbil model of transient global ischemia, compound reduced infarct size by 80%.

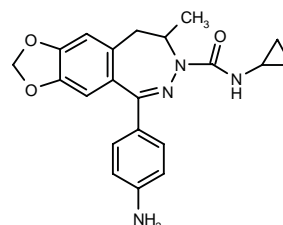
SOURCE – Cephalon.

REFERENCES

- Bihovsky, R. et al. (Cephalon, Inc.) *Benzothiazine and related heterocyclic group-containing cysteine and serine protease*. WO 9821186.
- Bihovsky, R. et al. *P2–P3 1,2-benzothiazine 1,1-dioxide peptide mimetic calpain I inhibitors*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 010.

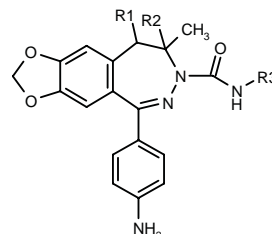
273859

(±)-5-(4-Aminophenyl)-*N*-cyclopropyl-8-methyl-8,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine-7-carboxamide



C₂₁ H₂₂ N₄ O₃; Mol wt: 378.4298

ACTION – An AMPA/kainate receptor antagonist with potential as a muscle relaxant, neuroprotective agent and anticonvulsant. AMPA-antagonist activity was demonstrated *in vitro* in the population spike test (100% inhibition at 10 μM) and in the spreading depression test (IC₅₀ = 1.3 μM). Muscle relaxant effects were demonstrated in mice following i.p. administration (ED₅₀ = 21.1 mg/kg), with a duration of action of > 2 h. Anticonvulsant activity was shown in mice in the maximal electroshock seizure (MES) test (ED₅₀ = 4.6 mg/kg i.p.), as well as in the audiogenic seizure test where it inhibited both clonic seizures and tonic extensor convulsions (ED₅₀ = 2.5 and 1.6 mg/kg i.p., respectively). Neuroprotective activity was demonstrated in the magnesium chloride-induced global ischemia test in mice (ID₅₀ = 13 mg/kg i.p.). A representative compound from a series of [1,3]dioxolo[4,5-*h*][2,3]benzodiazepine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
274855	bond		Me	C ₁₉ H ₁₈ N ₄ O ₃
273860	H	H	OMe	C ₁₉ H ₂₀ N ₄ O ₄
273862	H	H	NH ₂	C ₁₈ H ₁₉ N ₅ O ₃
273863	H	H	4-morpholinyl-CH ₂ CH ₂	C ₂₄ H ₂₉ N ₅ O ₄

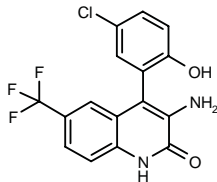
SOURCE – Egis.

REFERENCES

- Barkóczy, J. et al. (Egis Pharmaceuticals Ltd.) *1,3-Dioxolo[4,5-*h*][2,3]benzodiazepine derivs. as AMPA/kainate receptor inhibitors*. WO 9907708.

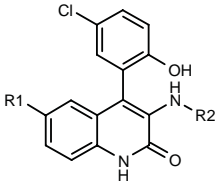
274098

3-Amino-4-(5-chloro-2-hydroxyphenyl)-6-(trifluoromethyl)-quinolin-2(1*H*)-one



C16 H10 Cl F3 N2 O2; Mol wt: 354.7140

ACTION – A potent BK_{Ca} (high-conductance, calcium-activated K⁺, Maxi-K) channel opener claimed for use in the treatment of ischemia, convulsions, asthma, irritable bowel syndrome, migraine, traumatic brain injury, male erectile dysfunction and urinary incontinence. At 0.001 mg/kg i.v. it produced a 14% reduction in cortical infarct volume in a focal stroke model involving permanent occlusion of the middle cerebral artery in spontaneously hypertensive rats. Within this series of specifically claimed 4-aryl-3-aminoquinoline-2-one derivatives, the following are also included:



Compound	R1	R2	Formula
274099	CF3	SO2CF3	C ₁₇ H ₉ ClF ₈ N ₂ O ₄ S
274100	CF3	CO2CH2Ph	C ₂₄ H ₁₆ ClF ₃ N ₂ O ₄
274102	CF3	4-NO2-PhSO2	C ₂₂ H ₁₃ ClF ₃ N ₃ O ₆ S
274103	CF3	4-F-PhSO2	C ₂₂ H ₁₃ ClF ₄ N ₂ O ₄ S
274104	NO2	H	C ₁₅ H ₁₀ ClN ₃ O ₄

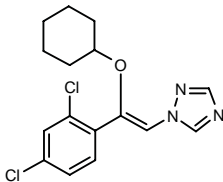
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Hewawasam, P. et al. (Bristol-Myers Squibb Co.) 4-Aryl-3-aminoquinoline-2-one derivs. as potassium channel modulators. WO 9909983.

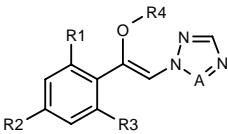
274124

1-[(*Z*)-2-(Cyclohexyloxy)-2-(2,4-dichlorophenyl)vinyl]-1*H*-1,2,4-triazole



C16 H17 Cl2 N3 O; Mol wt: 338.2363

ACTION – Neuronal injury inhibitor with affinity for group II metabotropic glutamate receptors (mGluR2 and mGluR3), giving a K_i value of 0.1 μM in a receptor binding assay using rat mGluR2 receptors. Other specifically claimed heterocyclic vinyl ether derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
274113	Cl	Cl	H	i-Bu	CH	C ₁₄ H ₁₅ Cl ₂ N ₃ O
274114	H	Br	H	Bu	CH	C ₁₄ H ₁₆ BrN ₃ O
274115	H	Cl	H	Bu	CH	C ₁₄ H ₁₆ ClN ₃ O
274116	Cl	H	Cl	Bu	CH	C ₁₄ H ₁₅ Cl ₂ N ₃ O
274119	Cl	Cl	H	CH2Ph	CH	C ₁₇ H ₁₃ Cl ₂ N ₃ O
274121	H	Cl	H	Bu	N	C ₁₃ H ₁₅ ClN ₄ O
274122	Cl	Cl	H	COPh	N	C ₁₆ H ₁₀ Cl ₂ N ₄ O ₂
274123	Cl	Cl	H	CH2Ph	N	C ₁₆ H ₁₂ Cl ₂ N ₄ O

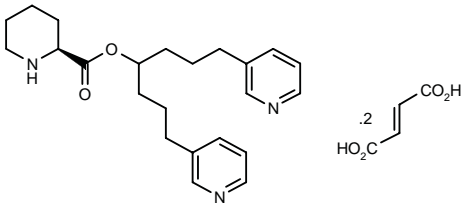
SOURCE – Roche.

REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) Heterocyclic vinyl ethers against neurological disorders. WO 9908678.

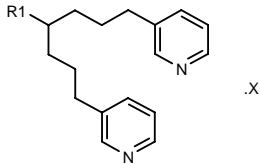
274545

Piperidine-2(*S*)-carboxylic acid 4-(3-pyridyl)-1-[3-(3-pyridyl)propyl]butyl ester difumarate

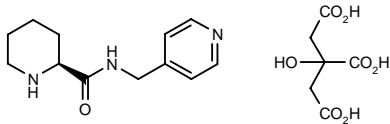


C23 H31 N3 O2 . 2 C4 H4 O4; Mol wt: 613.6601

ACTION – Neurotrophic agent shown to potently increase neurite outgrowth in pheochromocytoma PC12 cells at concentrations in the range 0.01-10 nM. Compound is reported to be specific for neuronal activity; it is devoid of immunosuppressive activity and does not bind to FK-506-binding protein (FKBP). Other exemplified compounds include the following:



Compound	R1	R2	Formula
274548	Me-L-Phe-N(Me)-	citrate	C ₂₈ H ₃₆ N ₄ O ₇ C ₆ H ₈ O ₇
274549	1-Me-2(<i>S</i>)-Pip-COO		C ₂₄ H ₃₃ N ₃ O ₂



274547: C12 H17 N3 O . C6 H8 O7

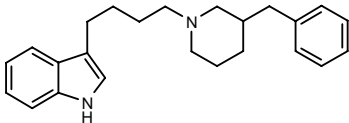
SOURCE – Vertex.

REFERENCES

1. Mccaffrey, P. et al. (Vertex Pharmaceuticals Inc.) *Cpds. possessing neuronal activity*. WO 9910340.

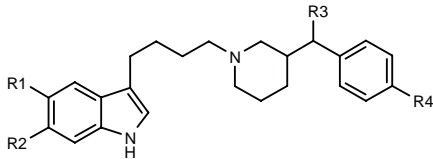
274634

3-[4-(3-Benzylpiperidin-1-yl)butyl]-1*H*-indole



C24 H30 N2; Mol wt: 346.5150

ACTION – Potent σ -receptor ligand and 5-HT reuptake inhibitor with potential in the treatment of CNS disorders, cerebrovascular accidents, craniocerebral or spinal cord injuries and ischemic conditions. Within this series of specifically claimed 3-benzylpiperidine derivatives, the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
274635	F	H	H	H		C ₂₄ H ₂₉ FN ₂
274636	CO ₂ H	H	H	H		C ₂₅ H ₃₀ N ₂ O ₂
274637	CO ₂ Me	H	H	H	R	C ₂₆ H ₃₂ N ₂ O ₂
274638	F	H	H	F		C ₂₄ H ₂₈ F ₂ N ₂
274639	-OCH ₂ O-		H	H	S	C ₂₅ H ₃₀ N ₂ O ₂
274640	CN	H	OH	F		C ₂₅ H ₂₈ FN ₃ O

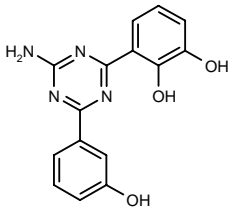
SOURCE – Merck KGaA.

REFERENCES

1. Böttcher, H. et al. (Merck Patent GmbH) *3-Benzylpiperidine*. WO 9857953.

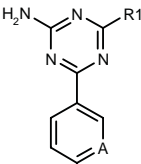
274978

3-[4-Amino-6-(3-hydroxyphenyl)-1,3,5-triazin-2-yl]benzene-1,2-diol



C15 H12 N4 O3; Mol wt: 296.2848

ACTION – Adenosine antagonist with high affinity for human A₁ receptors (K_i = 1.7 nM) and potential in the treatment of neurodegenerative disorders and depression. Other exemplified compounds from this series of triazine derivatives include the following:



Compound	R1	A	Formula
274979	3-OH-Ph	C(OH)	C ₁₅ H ₁₂ N ₄ O ₂
274980	3,5-(OH)2-Ph	C(OH)	C ₁₅ H ₁₂ N ₄ O ₃
274981	3,5-(OH)2-Ph	CH	C ₁₅ H ₁₂ N ₄ O ₂
274982	3-(MeOCH2)-Ph	CH	C ₁₇ H ₁₆ N ₄ O
274983	3-NO2-Ph	CH	C ₁₅ H ₁₁ N ₅ O ₂
274984	3-Me-2-furyl	N	C ₁₃ H ₁₁ N ₅ O

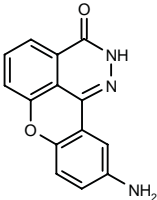
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Küfner-Mühl, U. et al. (Boehringer Ingelheim Pharma KG) *Triazines with an adenosine antagonistic effect*. WO 9911633.

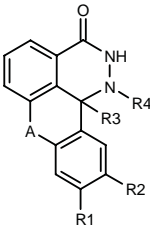
275164

10-Amino-1-benzopyran[4,3,2-*de*]phthalazin-3(2*H*)-one



C14 H9 N3 O2; Mol wt: 251.2441

ACTION – Neuroprotective agent, a potent inhibitor of NAD⁺ ADP-ribosyltransferase, also known as poly(adenosine diphosphate ribose) polymerase or poly(ADP) polymerase (PARP; IC₅₀ = 0.046 μ M against human recombinant enzyme). Also reported to be useful for the treatment or prevention of cardiovascular disorders, macular degeneration, arthritis, atherosclerosis, cachexia, cancer, diabetes, head trauma, inflammatory bowel disease, osteoporosis and septic shock. Other specifically claimed polycyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
275165	H	H	bond		O	C ₁₄ H ₈ N ₂ O ₂
275166	NH ₂	H	bond		bond	C ₁₄ H ₉ N ₃ O
275167	NO ₂	H	bond		bond	C ₁₄ H ₇ N ₃ O ₃
275168	NO ₂	H	bond		O	C ₁₄ H ₇ N ₃ O ₄
275169	NH ₂	N(Me)2	bond		O	C ₁₆ H ₁₄ N ₄ O ₂
275170	H	H	H	Me	O	C ₁₅ H ₁₂ N ₂ O ₂

SOURCE – Guilford.

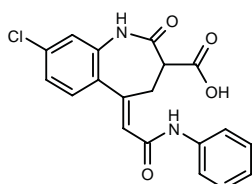
REFERENCES

1. Li, J.-H. et al. (Guilford Pharmaceuticals Inc.) *Poly(ADP-ribose) polymerase ("PARP") inhibitors, methods and pharmaceutical compsns. for treating neural or cardiovascular tissue damage*. WO 9911645.

GV-224029

274125

8-Chloro-5-(phenylcarbamoylmethylene)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-3-carboxylic acid



C₁₉ H₁₅ Cl N₂ O₄; Mol wt: 370.7905

ACTION – Glycine antagonist, a benzazepine derivative with neuroprotective activity in rats subjected to middle cerebral artery occlusion.

SOURCE – Glaxo Wellcome.

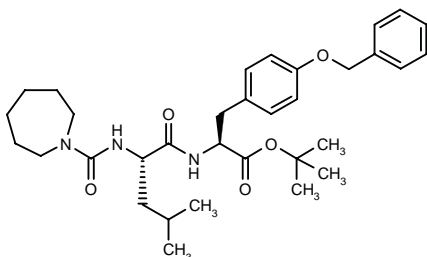
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1. Di Fabio, R. et al. *SAR and neuroprotective activity of a novel class of glycine antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 278.

PD-151307

274127

Perhydroazepin-1-ylcarbonyl-L-leucyl-O-(benzyl)-L-tyrosine *tert*-butyl ester



C₃₃ H₄₇ N₃ O₅; Mol wt: 565.7503

ACTION – Calcium channel blocker with an IC₅₀ value of 0.22 μM for N-type calcium channels in human IMR32 cells, showing about 40-fold selectivity for N- over L-type calcium channels (IC₅₀ = 9.1 μM in GH3 cells). Potentially useful in the treatment of cerebral ischemia and chronic intractable pain.

SOURCES – Neurex; Warner-Lambert.

REFERENCES

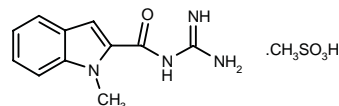
1. Malone, T. et al. *Identification and SAR studies of PD 151307, a novel N-type calcium channel blocker*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 122.

SM-20220*

261665

216252 (as hydrochloride)

N-(1-Methyl-1*H*-indol-2-ylcarbonyl)guanidine methanesulfonate



C₁₁ H₁₂ N₄ O . C H₄ O₃ S; Mol wt: 312.3484

ACTION – Potent and selective Na⁺/H⁺ exchange (NHE) inhibitor (IC₅₀ = 5 and 20 nM for inhibition of intracellular pH recovery after acidic load in cultured rat neuronal and glial cells, respectively) with potential in the treatment of ischemic stroke. Compound demonstrated good neuroprotective activity in rat models of both transient and permanent cerebral ischemia; in transient ischemia, it reduced infarct size and cerebral water and sodium content when administered 1 h after occlusion at doses of 0.3-1 mg/kg i.v., and in permanent ischemia, it exhibited protective activity when administered at a dose of 1 mg/kg i.v. 5, 30 or 60 min postocclusion.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Kojima, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Indolylguanidine derivs. as inhibitors of sodium-hydrogen exchange*. CA 2121391, EP 622356, JP 95010839.

2. Itoh, N. et al. *Effect of SM-20220, a novel Na⁺/H⁺ exchanger inhibitor, on cerebral ischemia*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-474.

3. Kuribayashi, Y. et al. *Delayed treatment with SM-20220, a potent Na⁺/H⁺ exchange inhibitor attenuates the brain damage following focal ischemia in rats*. Jpn J Pharmacol 1999, 79(Suppl. 1): Abst P-429.

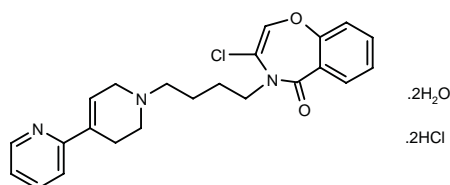
*Identified compound **216252** Drug Data Report 1995, 017(03): 0255.

SUN-N4057*

273884

240964 (as anhydrous free base)

3-Chloro-4-[4-[4-(2-pyridyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one dihydrochloride dihydrate



C₂₃ H₂₄ Cl N₃ O₂ . 2HCl . 2H₂O; Mol wt: 518.8660

ACTION – Neuroprotective agent, a potent and selective 5-HT_{1A} receptor agonist with partial agonist activity at the postsynaptic 5-HT_{1A} receptor negatively coupled to adenylate cyclase. In a rat model of transient focal cerebral ischemia, compound given immediately after occlusion (0.1-1 mg/kg s.c.) dose-dependently reduced both neuronal damage (63%) and ischemic hyperthermia. In the rat thrombotic middle cerebral artery occlusion model, compound infused for 4 h beginning immediately after occlusion significantly reduced the cortical infarct area by 19% (3 µg/kg/min) and 31% (6 µg/kg/min), but was ineffective when the start of infusion was delayed 3 h. Potentially useful for the treatment of acute ischemic stroke.

SOURCE – Suntory.

REFERENCES

1. Tatsuoaka, T. et al. (Suntory Ltd.) *Benzoxazepine derivs., salts thereof, and drugs containing the same*. EP 755930, WO 9624594.

2. Inoue, T. et al. *SUN N4057, a novel neuroprotectant, strongly attenuates neuronal damage induced by transient focal cerebral ischemia in rats*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-427.

3. Koyama, M. et al. *Effect of SUN N4057, a novel neuroprotectant, on cerebral infarction induced by thrombotic middle cerebral artery occlusion in rats*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-440.

4. *Suntory initiates clinical testing of three new compounds*. DailyDrugNews.com (Daily Essentials) 1998, June 17.

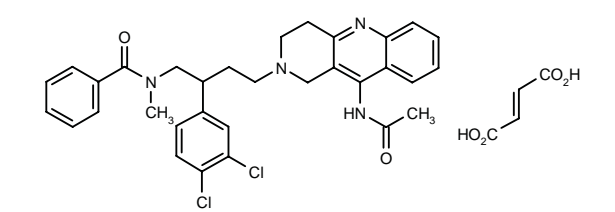
*Identified compound **240964** Drug Data Report 1997, 019(01): 0023.

RESPIRATORY DRUGS

ASTHMA THERAPY

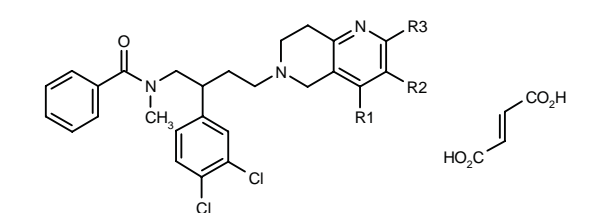
273498

(-)-N-[4-(10-Acetamido-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridin-2-yl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide fumarate



C32 H32 Cl2 N4 O2 · C4 H4 O4; Mol wt: 691.6084

ACTION – Potent tachykinin NK₂ receptor antagonist with an IC₅₀ value of 18 nM against [¹²⁵I]-neurokinin A binding in rat duodenum preparations. *In vivo*, it inhibited Nleu¹⁰-NKA (4-10)-induced bronchoconstriction in guinea pigs, giving 100.0 and 81.5% inhibition at 0.5 µmol/kg i.v. and 8 µmol/kg p.o., respectively. Other compounds from this series of naphthyridine derivatives include the following:



Compound	R1	R2,R3	Isomer	Formula
273499	H	-(CH2)4-	(-)	C ₃₀ H ₃₃ Cl ₂ N ₃ O ₃ ·C ₄ H ₄ O ₄
273500	CONH2	-CH=CHCH=CH-	(-)	C ₃₀ H ₂₉ Cl ₂ N ₃ O ₃ ·C ₄ H ₄ O ₄
273501	CO2Me	-CH=CHCH=CH-	(-)	C ₃₂ H ₃₁ Cl ₂ N ₃ O ₃ ·C ₄ H ₄ O ₄

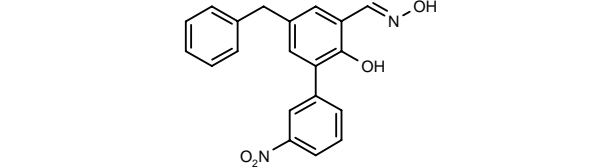
SOURCE – Nippon Kayaku.

REFERENCES

1. Oka, H. et al. (Nippon Kayaku Co., Ltd.) *Novel naphthyridine derivs. or salts thereof*. WO 9900388.

273919

5-Benzyl-2-hydroxy-3'-nitrophenyl-3-carbaldehyde oxime



C20 H16 N2 O4; Mol wt: 348.3564

ACTION – Antiasthmatic and antiinflammatory agent, a phosphodiesterase type 4 (PDE4) inhibitor, a representative compound from a series of biphenyl derivatives.

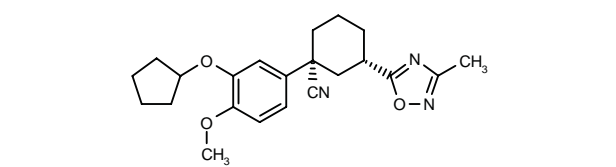
SOURCE – ADIR.

REFERENCES

1. Dhainaut, A. et al. (ADIR et Cie.) *Substd. biphenyl cpds*. US 5877190.

274130

1(*R*)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(*S*)-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexanecarbonitrile



C22 H27 N3 O3; Mol wt: 381.4733

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with about 3-fold selectivity for the LPDE4 over the HPDE4 form of the enzyme (IC₅₀ = 9 and 31 nM, respectively). In sensitized guinea pigs, compound attenuated ovalbumin-induced bronchoconstriction with an IC₅₀ of 2 mg/kg i.v. Potentially useful for the treatment of bronchial asthma.

ACTION – Neuroprotective agent, a potent and selective 5-HT_{1A} receptor agonist with partial agonist activity at the postsynaptic 5-HT_{1A} receptor negatively coupled to adenylate cyclase. In a rat model of transient focal cerebral ischemia, compound given immediately after occlusion (0.1-1 mg/kg s.c.) dose-dependently reduced both neuronal damage (63%) and ischemic hyperthermia. In the rat thrombotic middle cerebral artery occlusion model, compound infused for 4 h beginning immediately after occlusion significantly reduced the cortical infarct area by 19% (3 µg/kg/min) and 31% (6 µg/kg/min), but was ineffective when the start of infusion was delayed 3 h. Potentially useful for the treatment of acute ischemic stroke.

SOURCE – Suntory.

REFERENCES

1. Tatsuoaka, T. et al. (Suntory Ltd.) *Benzoxazepine derivs., salts thereof, and drugs containing the same*. EP 755930, WO 9624594.

2. Inoue, T. et al. *SUN N4057, a novel neuroprotectant, strongly attenuates neuronal damage induced by transient focal cerebral ischemia in rats*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-427.

3. Koyama, M. et al. *Effect of SUN N4057, a novel neuroprotectant, on cerebral infarction induced by thrombotic middle cerebral artery occlusion in rats*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-440.

4. *Suntory initiates clinical testing of three new compounds*. DailyDrugNews.com (Daily Essentials) 1998, June 17.

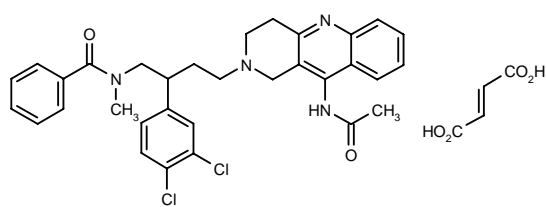
*Identified compound **240964** Drug Data Report 1997, 019(01): 0023.

RESPIRATORY DRUGS

ASTHMA THERAPY

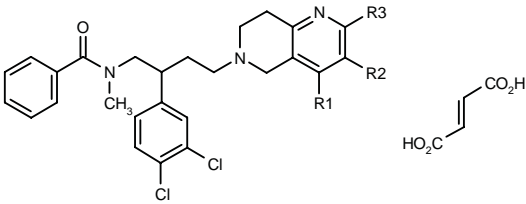
273498

(-)-N-[4-(10-Acetamido-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridin-2-yl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide fumarate



C32 H32 Cl2 N4 O2 . C4 H4 O4; Mol wt: 691.6084

ACTION – Potent tachykinin NK₂ receptor antagonist with an IC₅₀ value of 18 nM against [¹²⁵I]-neurokinin A binding in rat duodenum preparations. *In vivo*, it inhibited Nleu¹⁰-NKA (4-10)-induced bronchoconstriction in guinea pigs, giving 100.0 and 81.5% inhibition at 0.5 µmol/kg i.v. and 8 µmol/kg p.o., respectively. Other compounds from this series of naphthyridine derivatives include the following:



Compound	R1	R2,R3	Isomer	Formula
273499	H	-(CH2)4-	(-)	C ₃₀ H ₃₃ Cl ₂ N ₃ O ₃ .C ₄ H ₄ O ₄
273500	CONH2	-CH=CHCH=CH-	(-)	C ₃₀ H ₂₉ Cl ₂ N ₃ O ₃ .C ₄ H ₄ O ₄
273501	CO2Me	-CH=CHCH=CH-	(-)	C ₃₂ H ₃₁ Cl ₂ N ₃ O ₃ .C ₄ H ₄ O ₄

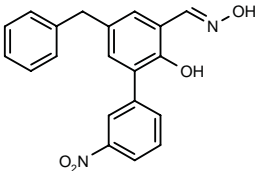
SOURCE – Nippon Kayaku.

REFERENCES

1. Oka, H. et al. (Nippon Kayaku Co., Ltd.) *Novel naphthyridine derivs. or salts thereof*. WO 9900388.

273919

5-Benzyl-2-hydroxy-3'-nitrophenyl-3-carbaldehyde oxime



C20 H16 N2 O4; Mol wt: 348.3564

ACTION – Antiasthmatic and antiinflammatory agent, a phosphodiesterase type 4 (PDE4) inhibitor, a representative compound from a series of biphenyl derivatives.

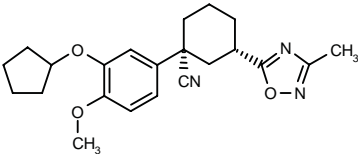
SOURCE – ADIR.

REFERENCES

1. Dhainaut, A. et al. (ADIR et Cie.) *Substd. biphenyl cpds*. US 5877190.

274130

1(*R*)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(*S*)-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexanecarbonitrile



C22 H27 N3 O3; Mol wt: 381.4733

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with about 3-fold selectivity for the LPDE4 over the HPDE4 form of the enzyme (IC₅₀ = 9 and 31 nM, respectively). In sensitized guinea pigs, compound attenuated ovalbumin-induced bronchoconstriction with an IC₅₀ of 2 mg/kg i.v. Potentially useful for the treatment of bronchial asthma.

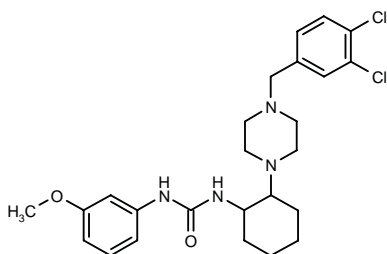
SOURCE – SmithKline Beecham.

REFERENCES

1. Christensen, S.B. IV and Forster, C.J. (SmithKline Beecham plc) 3-Cyano-3-(3,4-disubst.d.)phenylcyclohexyl-1-carboxylates. EP 714293, JP 97501420, WO 9503794.
2. Forster, C.J. et al. A comparison of the PDE4 activities of Ariflo™ (SB 207499) with those of 1,3-substituted cyclohexane carboxylate analogs. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 201.

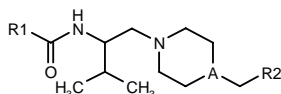
274766

N-[2-[4-(3,4-Dichlorobenzyl)-1-piperazinyl]cyclohexyl]-*N'*-(3-methoxyphenyl)urea



C25 H32 Cl2 N4 O2; Mol wt: 491.4598

ACTION – Antiasthmatic agent that acts as a chemokine CCR3 receptor antagonist ($IC_{50} = 0.69 \mu M$ against [^{125}I]-eotaxin binding in CCR3-transfected L1.2 cells). Compound also inhibits eotaxin-mediated chemotaxis of CCR3-transfected L1.2 cells ($IC_{50} = 0.46 \mu M$) and human eosinophils, and was active *in vivo* in inhibiting antigen-induced eosinophil influx into the lungs of sensitized mice. Within this series of cyclic amine derivatives, the following are also included.



Compound	R1	R2	A	Isomer	Formula
274767	2,4,6-(Me)3-PhNH	3,4-(Cl)2-Ph	N	R	C ₂₆ H ₃₆ Cl ₂ N ₄ O
274768	4-Me-Ph	4-NH2-5-Cl-2-MeO-PhCONH	CH		C ₂₇ H ₃₇ ClN ₄ O ₃

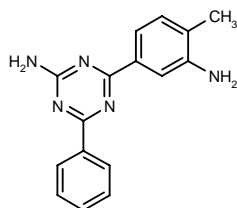
SOURCE – Roche.

REFERENCES

1. Gong, L. et al. (F. Hoffmann-La Roche AG) CCR-3 receptor antagonists. EP 903349.

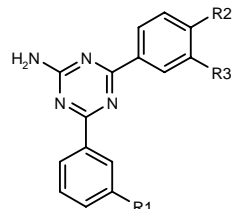
274974

4-(3-Amino-4-methylphenyl)-6-phenyl-1,3,5-triazin-2-amine



C16 H15 N5; Mol wt: 277.3295

ACTION – Adenosine antagonist with high affinity for human A₃ receptors ($K_i = 2.3 \text{ nM}$) and potential in the treatment of asthma, allergic rhinitis, myocardial reperfusion injury, as well as inflammatory and autoimmune disorders. Other exemplified compounds from this series of triazine derivatives include the following:



Compound	R1	R2	R3	Formula
274975	NHMe	H	NHMe	C ₁₇ H ₁₈ N ₆
274976	OH	Cl	H	C ₁₅ H ₁₁ ClN ₄ O
274977	OH	Me	H	C ₁₆ H ₁₄ N ₄ O

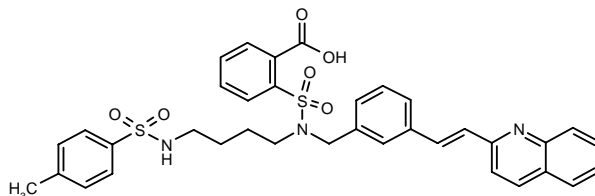
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Küfner-Mühl, U. et al. (Boehringer Ingelheim Pharma KG) Triazines with an adenosine antagonistic effect. WO 9911633.

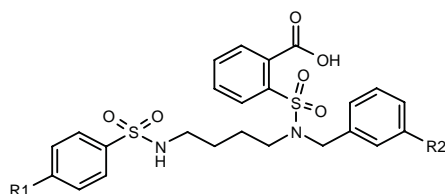
274986

2-[*N*-[4-(4-Methylphenylsulfonamido)butyl]-*N*-[3-(*E*)-(2-quinolinyl)vinyl]benzyl]sulfamoyl]benzoic acid



C36 H35 N3 O6 S2; Mol wt: 669.8195

ACTION – Antiallergic and antiasthmatic agent with dual LTD₄ (CysLT₁) receptor- and TxA₂ receptor-antagonist activity, shown to antagonize ovalbumin-induced bronchoconstriction in sensitized guinea pigs pretreated with pyrilamine (59.5% inhibition at 3 mg/kg i.v.). A representative compound from a series of 2-sulfamoylbenzoic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
274987	Cl	4- <i>i</i> -Pr-2-thiazolyl-CH ₂ O	C ₃₁ H ₃₄ ClN ₃ O ₇ S ₃
274988	Me	4-cyclopropyl-2-thiazolyl-CH ₂ O	C ₃₂ H ₃₆ N ₃ O ₇ S ₃
274989	Br	2-quinolinyl-CH ₂ CH ₂	C ₃₆ H ₃₄ BrN ₃ O ₆ S ₂

SOURCE – Kaken.

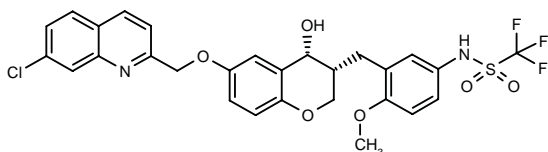
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1. Ichikawa, Y. et al. (Kaken Pharmaceutical Co., Ltd.) *2-Sulfamoylbenzoic acid derivs.* WO 9857935.

CP-199330

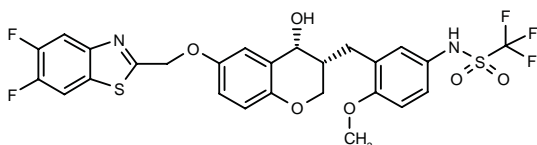
274091

N-[3-[6-(7-Chloro-2-quinolinylmethoxy)-4(*R*)-hydroxy-3,4-dihydro-2*H*-1-benzopyran-3(*S*)-ylmethyl]-4-methoxyphenyl]-trifluoromethanesulfonamide



C28 H24 Cl F3 N2 O6 S; Mol wt: 609.0186

ACTION – High-affinity LTD₄ (CysLT₁) antagonist, as shown in binding studies using receptors derived from guinea pig lung ($K_i = 0.6$ nM) and in a functional assay by blocking extracellular calcium influx in human U937 cells ($IC_{50} = 0.7$ nM). *In vivo*, compound was effective after oral administration in guinea pig models of asthma, blocking both antigen- and LTD₄-induced airways obstruction with ED₅₀ values of 0.46 and 0.12 mg/kg, respectively, at 1 h. Compound exhibited a good pharmacokinetic profile in rat and monkey, with low hepatic clearance and high oral bioavailability (53 and 100% in rats and monkeys, respectively). Potentially useful for the treatment of bronchial asthma. Another related compound is:



CP-199331 [274092]: C26 H21 F5 N2 O6 S2

SOURCE – Pfizer.

REFERENCES

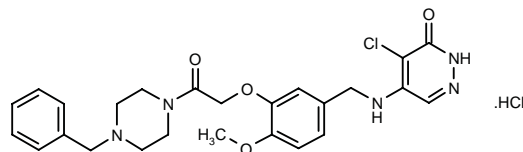
1. Marfat, A. (Pfizer Inc.) *Sulfonamide derivs. of benzenefused hydroxy subst. cycloalkyl and heterocyclic ring cpds.* EP 665842, JP 95508534, US 5641789, WO 9408996.

2. Chambers, R.J. et al. *Discovery of CP-199,330 and CP-199,331, two potent, orally bioavailable and efficacious antagonists of leukotriene D₄.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 204.

NIP-520*

221150

5-[3-[2-(4-Benzylpiperazin-1-yl)-2-oxoethoxy]-4-methoxybenzylamino]-4-chloropyridazin-3(2*H*)-one hydrochloride



C25 H28 Cl N5 O4 . HCl; Mol wt: 534.4470

ACTION – Antiasthmatic agent, a pyridazinone derivative with potent relaxant activity *in vitro* in human bronchial and guinea pig tracheal smooth muscle (110- and 230-fold more potent than theophylline, respectively). Compound attenuated IL-5-induced eosinophil survival, selectively inhibited phosphodiesterase type 3 (PDE3) derived from guinea pig trachea and suppressed mitogen-induced human airways smooth muscle cell proliferation. *In vivo* in sensitized guinea pigs, it inhibited both antigen-induced airways hyperresponsiveness and inflammation and prevented early- and late-phase airways responses at doses of 3-10 mg/kg p.o.

SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Pyridazinone derivs. with pharmaceutical activity.* EP 706517, JP 96041033, US 5728702, WO 9501343.

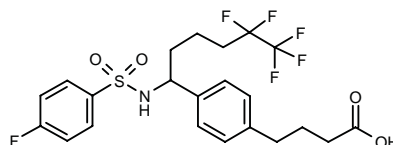
2. Iwama, T. et al. *Pharmacological profiles of a novel antiasthmatic agent, NIP-520.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-660.

*Identified compound **221150** (see **218637**) Drug Data Report 1995, 017(05): 0426.

RS-635

273894

(+)-4-[4-[5,5,6,6-Pentafluoro-1-(4-fluorophenyl)sulfonamido)hexyl]phenyl]butanoic acid



C22 H23 F6 N O4 S; Mol wt: 511.4807

ACTION – Dual LTD₄ and TxA₂ antagonist, the (+)-enantiomer of the racemic RS-601⁺, proven to inhibit bronchoconstriction induced by LTD₄ or the TxA₂ agonist U-46619 in guinea pigs following oral administration. Compound was more effective in protecting against antigen-induced bronchoconstriction in passively sensitized guinea pigs as compared to specific LTD₄ or TxA₂ antagonists. Potentially useful for the treatment of bronchial asthma.

SOURCE – Hokuriku.

REFERENCES

1. Yasuda, S. et al. (Hokuriku Seiyaku Co., Ltd.) *Benzenesulfonamide derivs. and drugs containing the same*. JP 98195038, WO 9821177.

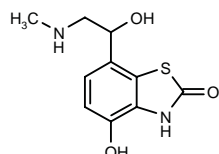
2. Ohashi, T. et al. *Pharmacological features of RS-635, a novel LTD4/TXA2 dual antagonist, in guinea-pigs*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-571.

*Drug Data Report 1998, 020(09): 0762.

S-1319

273887

4-Hydroxy-7-[1-hydroxy-2-(methylamino)ethyl]-2,3-dihydrobenzothiazol-2-one



C10 H12 N2 O3 S; Mol wt: 240.2818

ACTION – Short-acting, highly selective β_2 -adrenoceptor agonist extracted from the marine sponge *Dysidea* sp., with potent relaxant activity in guinea pig trachea ($pD_2 = 10.8$) superior to isoproterenol and salbutamol ($pD_2 = 7.2$ and 7.5 , respectively) and comparable to formoterol ($pD_2 = 10.6$). Compound showed good selectivity for tracheal muscle versus left atria, and the time to achieve maximal contraction *in vitro* was shorter ($t_{1/2} = 4$ min) as compared to isoproterenol, salbutamol and formoterol ($t_{1/2} = 7, 37$ and 48 min, respectively).

SOURCE – Kirin Brewery.

REFERENCES

1. Suzuki, H. et al. (Kirin Brewery Co., Ltd.) *Benzothiazolone derivs. having selective β_2 receptor agonist activity*. WO 9909018.

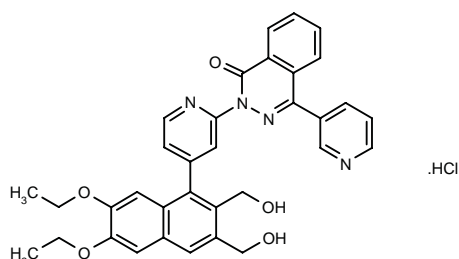
2. Suzuki, H. et al. *S1319: A novel β_2 -adrenoceptor agonist from a marine sponge *Dysidea* sp.* Bioorg Med Chem Lett 1999, 9(10): 1361.

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T-2585.HCl*

246245

2-[4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]pyridin-2-yl]-4-(3-pyridyl)phthalazin-1(2H)-one hydrochloride



C34 H30 N4 O5 . HCl; Mol wt: 611.0949

ACTION – Potent and selective inhibitor of phosphodiesterase type 4 (PDE4; $IC_{50} = 0.13$ nM) with more than 1500-fold selectivity over PDE1, PDE2, PDE3 and PDE5. *In vivo*, compound exhibited activity against both antigen- and histamine-induced bronchoconstriction in guinea pigs with ED_{50} values of 0.063 mg/kg i.v. and 0.033 mg/kg i.d., respectively, without inducing significant changes in heart rate. In comparison to the reference PDE4 inhibitor RP-73401, it was at least equipotent in both *in vitro* and *in vivo* models, but was associated with a reduced emetic effect after oral administration in ferrets and i.v. administration in dogs. Potentially useful as an antiasthmatic, antiallergic and antiinflammatory agent.

SOURCE – Tanabe.

REFERENCES

1. Ukida, S. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns*. JP 98226647.

2. Ukita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Naphthalene derivs., process for the preparation thereof, and pharmaceutical compsns. comprising them*. CA 2178974, EP 748805, JP 97059255.

3. Ukita, T. et al. *Novel, potent, and selective phosphodiesterase-4 inhibitors as antiasthmatic agents: Synthesis and biological activities of a series of 1-pyridylnaphthalene derivatives*. J Med Chem 1999, 42(6): 1088.

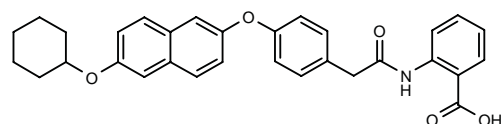
4. Ukita, T. et al. *The novel potent and selective PDE IV inhibitors*. 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst MEDI 091.

*Identified compound **246245** (see **245557**) Drug Data Report 1997, 019(04): 0314.

TEI-9874

273888

2-[4-[6-(Cyclohexyloxy)-2-naphthyloxy]phenylacetamido]-benzoic acid



C31 H29 N O5; Mol wt: 495.5721

ACTION – Antiasthmatic and antiallergic agent, an inhibitor of IgE production from peripheral blood mononuclear cells. Treatment with the compound ($3, 10$ or 30 mg/kg x 5 days p.o.) prior to antigen challenge in rats decreased the immediate and late asthmatic response, infiltration of inflammatory cells into bronchoalveolar lavage fluid, and serum antiovalbumin IgE levels. Compound (30 mg/kg p.o.) also prevented ovalbumin-induced airways hyperresponsiveness to acetyl- β -methylcholine in rats.

SOURCE – Teijin.

REFERENCES

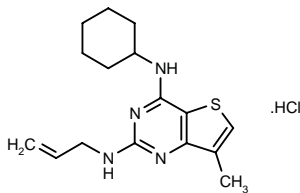
1. Takenouchi, K. et al. (Teijin Ltd.) *Naphthalene deriv.* EP 763523, WO 9532943.

2. Sugiyama, H. et al. *Inhibitory effect of TEI-9874, an inhibitor of IgE production, on allergen-induced biphasic asthmatic model in rats*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-575.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES (COPD)

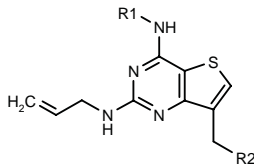
273954

N²-Allyl-N⁴-cyclohexyl-7-methylthieno[3,2-*d*]pyrimidine-2,4-diamine hydrochloride



C₁₆ H₂₂ N₄ S . HCl; Mol wt: 338.9047

ACTION – Agent for the treatment or prevention of hypoxemia in patients with respiratory insufficiency such as chronic obstructive pulmonary disease (COPD); it acts by increasing arterial blood oxygen partial pressure (PaO₂), as demonstrated in rats subjected to hypoxia, where it produced an increase in PaO₂ of 42 mmHg when given i.v. at 0.1 mg/kg/min. Other compounds from this series of fused pyrimidine derivatives include the following:



Compound	R1	R2	Formula
273955	t-Bu	H	C ₁₄ H ₂₀ N ₄ S
273956	Et	H	C ₁₂ H ₁₆ N ₄ S
273957	1-adamantyl	H	C ₂₀ H ₂₆ N ₄ S
273958	allyl	Me	C ₁₄ H ₁₈ N ₄ S
273959	t-Bu	Me	C ₁₅ H ₂₂ N ₄ S
273960	Me	Et	C ₁₃ H ₁₈ N ₄ S

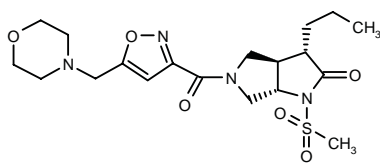
SOURCE – Fujirebio.

REFERENCES

1. Nakashima, Y. et al. (Fujirebio, Inc.) *Fused pyrimidine derivs. and medicaments thereof for a blood oxygen partial pressure amelioration*. EP 899263.

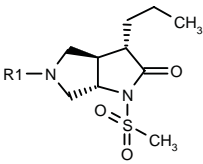
275287

(3*S**,3*aR**,6*aS**)-1-(Methylsulfonyl)-5-[5-(4-morpholinylmethyl)-3-isoxazolylcarbonyl]-3-propylperhydro-pyrrolo[3,4-*b*]pyrrol-2-one



C₁₉ H₂₈ N₄ O₆ S; Mol wt: 440.5182

ACTION – An inhibitor of human neutrophil elastase (IC₅₀ = 0.146 μM) with potential in the treatment of chronic bronchitis and chronic obstructive pulmonary disease (COPD). Other specifically claimed compounds from this series of pyrrolopyrrolone derivatives include the following:



Compound	R1	Formula
275288	(E)-1-Pip-CH ₂ CH=CHCO	C ₁₉ H ₃₁ N ₃ O ₄ S
275289	1-Pip-(CH ₂) ₃ CO	C ₁₉ H ₃₃ N ₃ O ₄ S
275290	4-(AcNH)-PhSO ₂	C ₁₈ H ₂₅ N ₃ O ₆ S ₂
275291	4-(1-Pip)-PhCO	C ₂₂ H ₃₁ N ₃ O ₄ S
275292	4-(4-morpholinyl-CH ₂)-PhCO	C ₂₂ H ₃₁ N ₃ O ₅ S
275293	5-N(Me)2-3-isoxazolyl-CO	C ₁₈ H ₂₄ N ₄ O ₅ S

SOURCE – Glaxo Wellcome.

REFERENCES

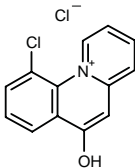
1. Dowle, M.D. et al. (Glaxo Group Ltd.) *Pyrrolopyrrolone derivs*. WO 9912934.

TREATMENT OF CYSTIC FIBROSIS

MPB-07*

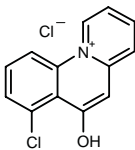
251255

10-Chloro-6-hydroxybenzo[*c*]quinolizinium chloride



C₁₃ H₉ Cl₂ N O; Mol wt: 266.1261

ACTION – Agent for the treatment of cystic fibrosis shown to activate cystic fibrosis transmembrane conductance regulator (CFTR) channels in transfected CHO cells and native pancreatic duct cells. Another substituted benzoquinolizinium compound is:



MPB-27 [274904]: C₁₃ H₉ Cl₂ N O

SOURCE – INSERM.

REFERENCES

1. Becq, F. et al. (CNRS [Centre Nat. Rech. Sci.]) *CFTR channel activator cpds. and pharmaceutical compsns. containing same*. WO 9805642.

2. Gray, M.A. et al. *Novel activators of CFTR in native epithelial cells*. FASEB J 1999, 13(4, Part 1): Abst 110.6.

3. Mettey, Y. and Vierfond, J.-M. *Benzo[c]quinoliziums: A new family of inhibitors for protein kinase CK II*. Bioorg Med Chem Lett 1997, 7(8): 961.

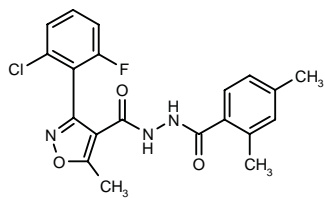
*Identified compound **251255** Drug Data Report 1997, 019(06): 0576.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

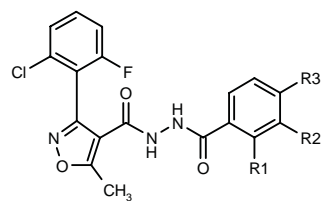
272780

N'-[3-(2-Chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl-carbonyl]-2,4-dimethylbenzohydrazide



C20 H17 Cl F N3 O3; Mol wt: 401.8233

ACTION – Agent for the treatment of angiotensin II-mediated disorders, a selective human chymase inhibitor (IC₅₀ = 70 μM) with no effect on human chymotrypsin (IC₅₀ > 1000 μM). Other exemplified compounds from this series of isoxazole derivatives include the following:



Compound	R1	R2	R3	Formula
272781	Me	Me	H	C ₂₀ H ₁₇ ClFN ₃ O ₃
272782	H	H	OMe	C ₁₉ H ₁₅ ClFN ₃ O ₄

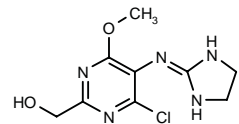
SOURCE – Nippon Steel.

REFERENCES

1. Ito, K. et al. (Nippon Steel Corp.) *Isooxazole derivs. having amido bond, chymase inhibitors containing them and angiotensin II production inhibitors*. JP 99001479.

274910

[4-Chloro-5-(imidazolidin-2-ylideneamino)-6-methoxy-2-pyrimidinyl]methanol



C9 H12 Cl N5 O2; Mol wt: 257.6798

ACTION – Moxonidine⁺ metabolite identified in the urine of rats, dogs and humans that has been found to possess analogous activities to the parent compound, in particular antihypertensive and bradycardic activity in conscious unrestrained hypertensive rats, with a duration of action of about 4 h. Claimed for the treatment of hypertension, congestive heart failure, non-insulin-dependent diabetes, smoking cessation, nicotine, opioid or alcohol withdrawal and atherosclerosis.

SOURCE – Lilly.

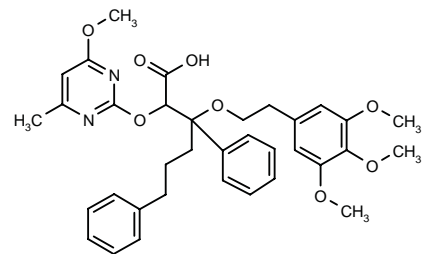
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1. Abraham, T.L. et al. (Eli Lilly and Company) *Pyrimidine derivs*. WO 9911269.

*Drug Data Rep 1992, 014(04): 0319.

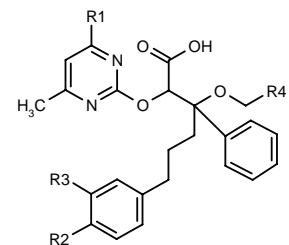
274950

2-(4-Methoxy-6-methyl-2-pyrimidinyl)-3,6-diphenyl-3-[2-(3,4,5-trimethoxyphenyl)ethoxy]hexanoic acid



C35 H40 N2 O8; Mol wt: 616.7070

ACTION – Mixed endothelin ET_A/ET_B receptor antagonist with K_i values of 13 and 15 nM, respectively. Potentially useful in the treatment of hypertension, myocardial infarction, angina pectoris, renal failure, cerebral vasospasm, cerebral ischemia, migraine, asthma, atherosclerosis, endotoxic shock, restenosis, benign prostatic hyperplasia, cancer, pancreatitis and gastrointestinal ulcers. Other compounds from this series of carboxylic acid derivatives include the following:



Compound	R1	R2=R3	R4	Formula
274952	Me	OMe	3,4-(MeO)2-Ph	C ₃₅ H ₄₀ N ₂ O ₈
274954	OMe	H	3,4-(MeO)2-PhCH ₂	C ₃₄ H ₃₈ N ₂ O ₇
274955	OMe	H	4-OH-3-MeO-PhCH ₂	C ₃₃ H ₃₆ N ₂ O ₇

REFERENCES

1. Becq, F. et al. (CNRS [Centre Nat. Rech. Sci.]) *CFTR channel activator cpds. and pharmaceutical compsns. containing same*. WO 9805642.

2. Gray, M.A. et al. *Novel activators of CFTR in native epithelial cells*. FASEB J 1999, 13(4, Part 1): Abst 110.6.

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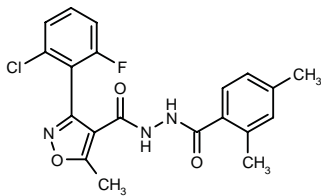
*Identified compound **251255** Drug Data Report 1997, 019(06): 0576.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

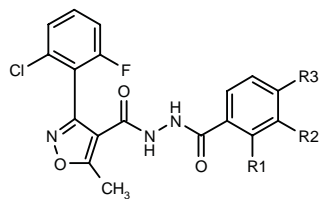
272780

N'-[3-(2-Chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl-carbonyl]-2,4-dimethylbenzohydrazide



C20 H17 Cl F N3 O3; Mol wt: 401.8233

ACTION – Agent for the treatment of angiotensin II-mediated disorders, a selective human chymase inhibitor (IC₅₀ = 70 μM) with no effect on human chymotrypsin (IC₅₀ > 1000 μM). Other exemplified compounds from this series of isoxazole derivatives include the following:



Compound	R1	R2	R3	Formula
272781	Me	Me	H	C ₂₀ H ₁₇ ClFN ₃ O ₃
272782	H	H	OMe	C ₁₉ H ₁₅ ClFN ₃ O ₄

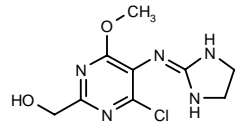
SOURCE – Nippon Steel.

REFERENCES

1. Ito, K. et al. (Nippon Steel Corp.) *Isooxazole derivs. having amido bond, chymase inhibitors containing them and angiotensin II production inhibitors*. JP 99001479.

274910

[4-Chloro-5-(imidazolidin-2-ylideneamino)-6-methoxy-2-pyrimidinyl]methanol



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ACTION – Moxonidine⁺ metabolite identified in the urine of rats, dogs and humans that has been found to possess analogous activities to the parent compound, in particular antihypertensive and bradycardic activity in conscious unrestrained hypertensive rats, with a duration of action of about 4 h. Claimed for the treatment of hypertension, congestive heart failure, non-insulin-dependent diabetes, smoking cessation, nicotine, opioid or alcohol withdrawal and atherosclerosis.

SOURCE – Lilly.

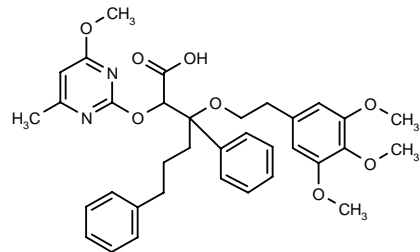
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*Drug Data Rep 1992, 014(04): 0319.

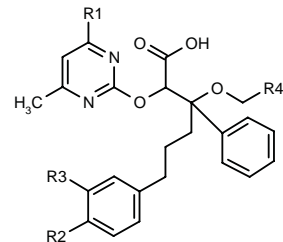
274950

2-(4-Methoxy-6-methyl-2-pyrimidinyl)-3,6-diphenyl-3-[2-(3,4,5-trimethoxyphenyl)ethoxy]hexanoic acid



C35 H40 N2 O8; Mol wt: 616.7070

ACTION – Mixed endothelin ET_A/ET_B receptor antagonist with K_i values of 13 and 15 nM, respectively. Potentially useful in the treatment of hypertension, myocardial infarction, angina pectoris, renal failure, cerebral vasospasm, cerebral ischemia, migraine, asthma, atherosclerosis, endotoxic shock, restenosis, benign prostatic hyperplasia, cancer, pancreatitis and gastrointestinal ulcers. Other compounds from this series of carboxylic acid derivatives include the following:



Compound	R1	R2=R3	R4	Formula
274952	Me	OMe	3,4-(MeO)2-Ph	C ₃₅ H ₄₀ N ₂ O ₈
274954	OMe	H	3,4-(MeO)2-PhCH ₂	C ₃₄ H ₃₈ N ₂ O ₇
274955	OMe	H	4-OH-3-MeO-PhCH ₂	C ₃₃ H ₃₆ N ₂ O ₇

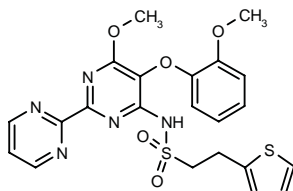
SOURCE – BASF.

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1. Amberg, W. et al. (BASF AG) *Novel carboxylic acid derivs., their production and their use as mixed ETA/ETB endothelin-receptor antagonists*. WO 9911629.

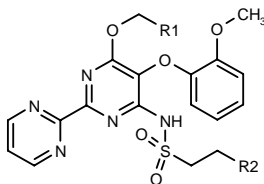
274991

N-[6-Methoxy-5-(2-methoxyphenyl)-2-(2-pyrimidinyl)-pyrimidin-4-yl]-2-(2-thienyl)ethanesulfonamide



C22 H21 N5 O5 S2; Mol wt: 499.5699

ACTION – Endothelin ET_A receptor antagonist, as demonstrated in a binding assay by an IC₅₀ value of 2.6 nM against [¹²⁵I]-ET-1 binding in COS-1 cells expressing the human ET_A receptor. A representative compound from a series of substituted sulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
274992	H	Ph	C ₂₄ H ₂₃ N ₅ O ₅ S
274993	CH ₂ OMe	Ph	C ₂₆ H ₂₇ N ₅ O ₆ S
274994	H	2-Naph	C ₂₈ H ₂₅ N ₅ O ₅ S
274995	H	4-Me-Ph	C ₂₅ H ₂₅ N ₅ O ₅ S

SOURCE – Yamanouchi.

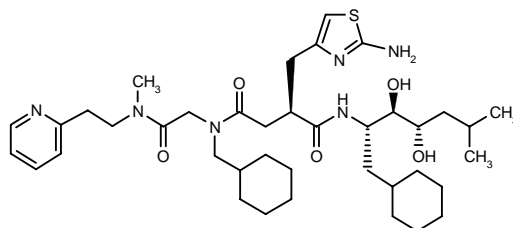
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BILA-2157-BS

266764

2(*R*)-(2-Aminothiazol-4-ylmethyl)-*N*⁴-(cyclohexylmethyl)-*N*¹-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*⁴-[*N*-methyl-*N*-[2-(2-pyridyl)ethyl]-carbamoylmethyl]succinamide



C39 H62 N6 O5 S; Mol wt: 727.0218

ACTION – Potent and specific, nonpeptide renin inhibitor (IC₅₀ = 1.4 and 2.5 nM at pH 6.0 and 7.4, respectively, vs. IC₅₀ = 540 nM for cathepsin D). In conscious, sodium-depleted cynomolgus monkeys, compound (3 and 10 mg/kg p.o.) significantly decreased mean arterial blood pressure and plasma angiotensin II levels, with no effect on heart rate. In conscious sodium-depleted dogs, BILA-2157-BS (10 mg/kg i.v.) significantly decreased total peripheral resistance. Compound showed a good pharmacokinetic profile in cynomolgus monkeys, with an oral bioavailability of 40%. Selected for further evaluation as a potential treatment for hypertension and congestive heart failure.

SOURCE – Boehringer Ingelheim.

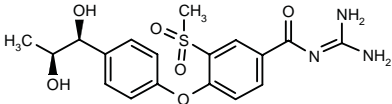
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2. Beaulieu, P.L. et al. *Practical, stereoselective chemo-enzymatic synthesis of BILA2157BS, a potent renin inhibitor*. 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst ORGN 026.
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4. Duan, J. et al. *Comparative studies on differential inhibition of the renin-angiotensin system in the anesthetized guinea pig*. Can J Physiol Pharmacol 1995, 73(10): 1512.
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7. Simoneau, B. et al. *Discovery of non-peptidic P2-P3 butanediamide renin inhibitors with high oral efficacy*. Bioorg Med Chem 1999, 7(3): 489.
8. Way, S.L. et al. *Preformulation studies for the renin inhibitor BILA 2157*. Pharm Res 1995, 12(9, Suppl.): Abst PDD 7037.

TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES
AND ATHEROSCLEROSIS

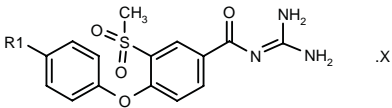
273947

N²-[4-[4-[(1*S*),2(*S*)-Dihydroxypropyl]phenoxy]-3-(methylsulfonyl)benzoyl]guanidine



C18 H21 N3 O6 S; Mol wt: 407.4449

ACTION – Cardiac antiischemic agent, an inhibitor of Na⁺/H⁺ exchange (IC₅₀ = 0.1-0.5 μM in rabbit erythrocytes) reported to be free of salidiuretic effects. Compound is also reported to inhibit the proliferation of cells such as fibroblasts and vascular smooth muscle cells and is therefore also expected to be useful in the treatment of atherosclerosis, cancer, fibrotic disorders and prostatic hyperplasia. Other compounds from this series of substituted benzoylguanidines include the following:



Compound	R1	X	Formula
273948	Ac	HCl	C ₁₇ H ₁₇ N ₃ O ₅ S.HCl
273949	CH(OH)Me	HCl	C ₁₇ H ₁₉ N ₃ O ₅ S.HCl
273950	(<i>R,R</i>)-CH(OH)CH(OH)Me		C ₁₈ H ₂₁ N ₃ O ₆ S

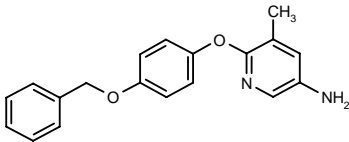
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Lang, H.-J. et al. (Hoechst AG) *Substd. benzoylguanidines, process for their preparation, their use as a medicament or diagnostic and medicament containing them.* US 5880156.

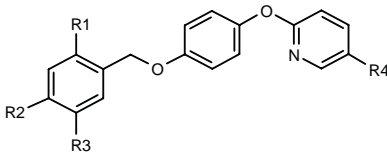
274671

6-[4-(Benzyloxy)phenoxy]-5-methylpyridin-3-amine



C19 H18 N2 O2; Mol wt: 306.3632

ACTION – Antiischemic agent with Na⁺/Ca²⁺ exchange-inhibitory activity (77% inhibition at 1 μM using membrane vesicles from canine ventricular muscle). Other representative compounds within this series of phenoxy pyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
274672	H	H	H	NO2	C ₁₈ H ₁₃ FN ₂ O ₄
274673	H	F	H	NO2	C ₁₈ H ₁₂ F ₂ N ₂ O ₄
274674	H	H	F	NO2	C ₁₈ H ₁₂ F ₂ N ₂ O ₄
274675	F	H	H	NO2	C ₁₈ H ₁₂ F ₂ N ₂ O ₄
274676	H	F	H	NH2	C ₁₈ H ₁₄ F ₂ N ₂ O ₂

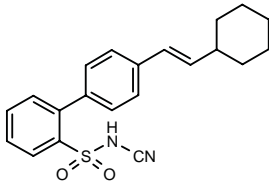
SOURCE – Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Phenoxy pyridine derivs.* JP 99049752.

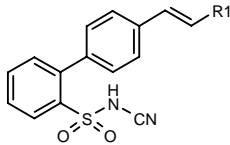
274757

(*E*)-*N*-Cyano-4'-(2-cyclohexylvinyl)biphenyl-2-sulfon-amide



C21 H22 N2 O2 S; Mol wt: 366.4828

ACTION – An inhibitor of Na⁺-dependent Cl⁻/HCO₃⁻ exchange (NCBE), as demonstrated in human endothelial cells, with cardioprotective and antiproliferative activity. Potentially useful for the treatment or prevention of ischemic disorders, myocardial infarction, angina pectoris, stroke, shock states, respiratory disorders and proliferative disorders. Other compounds form this series of biphenylsulfonylcyanamides include the following:



Compound	R1	Isomer	Formula
274759	Ph	E	C ₂₀ H ₂₂ N ₂ O ₂ S
274761	cyclohexyl	Z	C ₂₁ H ₁₈ N ₂ O ₂ S

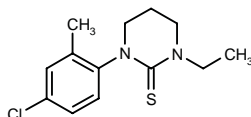
SOURCE – Hoechst Marion Roussel.

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1. Kleeman, H.-W. et al. (Hoechst Marion Roussel Deutschland GmbH) *Biphenylsulfonylcyanamides, process for their preparation and their use as medicaments.* EP 903339.

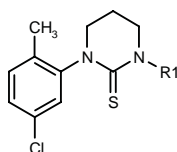
274944

1-(4-Chloro-2-methylphenyl)-3-ethylhexahydropyrimidine-2-thione



C₁₃H₁₇ClN₂S; Mol wt: 268.8103

ACTION – Agent for the treatment of atherosclerosis, coronary heart disease and dyslipoproteinemia, proven to elevate HDL cholesterol levels in cholesterol-fed rats by 151.5% when administered at 50 mg/kg/day p.o. x 8 days mixed with the diet. Other compounds from this series of substituted hexahydro-2-pyrimidinethione derivatives include the following:



Compound	R1	Formula
274946	Et	C ₁₃ H ₁₇ ClN ₂ S
274947	i-Pr	C ₁₄ H ₁₉ ClN ₂ S
274948	Me	C ₁₂ H ₁₅ ClN ₂ S

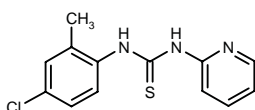
SOURCE – American Home Products.

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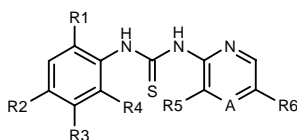
274958

N-(4-Chloro-2-methylphenyl)-N'-(2-pyridyl)thiourea



C₁₃H₁₂ClN₃S; Mol wt: 277.7778

ACTION – Agent for the treatment of atherosclerosis, coronary heart disease and dyslipoproteinemia, proven to elevate HDL cholesterol levels by 513% in cholesterol-fed rats when administered at 100 mg/kg/day p.o. x 8 days mixed with the diet. Other compounds from this series of substituted thiourea derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
274959	Me	H	Cl	H	H	H	N	C ₁₂ H ₁₁ ClN ₄ S
274960	Cl	H	H	Me	H	H	CH	C ₁₃ H ₁₂ ClN ₃ S
274961	Cl	H	H	Me	H	Cl	CH	C ₁₃ H ₁₁ Cl ₂ N ₃ S
274962	Me	H	Cl	H	Me	H	CH	C ₁₄ H ₁₄ ClN ₃ S
274963	Cl	H	H	Me	Me	H	CH	C ₁₄ H ₁₄ ClN ₃ S
274964	Me	Cl	H	H	Me	H	CH	C ₁₄ H ₁₄ ClN ₃ S

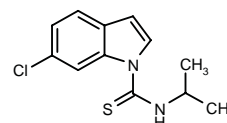
SOURCE – American Home Products.

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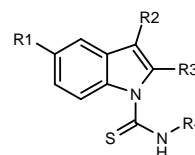
275046

6-Chloro-N-isopropyl-1H-indole-1-carbothioamide



C₁₂H₁₃ClN₂S; Mol wt: 252.7677

ACTION – Agent for the treatment of atherosclerosis, coronary heart disease and dyslipoproteinemia, proven to elevate HDL cholesterol levels by 66% in cholesterol-fed rats when administered at 100 mg/kg/day p.o. x 8 days mixed with the diet. Within this series of substituted 1H-indole-1-carbothioamide derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
275047	Cl	H	H	i-Pr	C ₁₂ H ₁₃ ClN ₂ S
275048	Cl	H	H	1,3,5-(Me)3-4-pyrazolyl	C ₁₅ H ₁₅ ClN ₄ S
275049	H	H	Me	5-Cl-2-Me-Ph	C ₁₇ H ₁₅ ClN ₂ S
275050	H	Me	Me	5-Cl-2-Me-Ph	C ₁₈ H ₁₇ ClN ₂ S

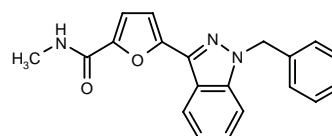
SOURCE – American Home Products.

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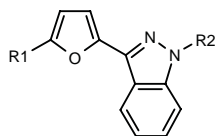
275051

5-(1-Benzyl-1H-indazol-3-yl)-N-methyl-2-furancarboxamide



C₂₀H₁₇N₃O₂; Mol wt: 331.3733

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris, thrombosis and atherosclerosis that acts by activating soluble guanylate cyclase, as demonstrated *in vitro* using enzyme isolated from bovine lung preparations at 100 μM. Other compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	Formula
275052	CH ₂ OH	3,5-(CF ₃) ₂ -Ph	C ₂₀ H ₁₂ F ₆ N ₂ O ₂
275053	CO ₂ CH ₂ CH ₂ OH	CH ₂ Ph	C ₂₁ H ₁₈ N ₂ O ₄
275054	CONHPh	CH ₂ Ph	C ₂₆ H ₁₉ N ₃ O ₂
275055	2-thiazolyl-NHCO	CH ₂ Ph	C ₂₂ H ₁₆ N ₄ O ₂ S
275056	ethynyl-CH(OH)	CH ₂ Ph	C ₂₁ H ₁₆ N ₂ O ₂

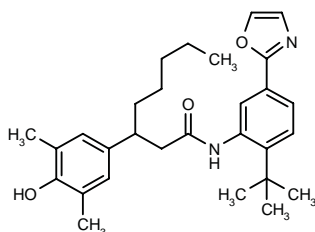
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Schindler, U. et al. (Hoechst Marion Roussel Deutschland GmbH) *Pyrazole derivs., their preparation and their use in drugs*. EP 908456.

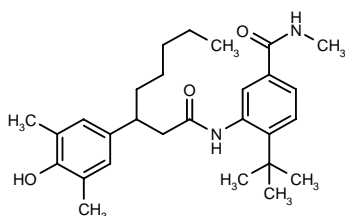
275071

N-[2-*tert*-Butyl-5-(2-oxazolyl)phenyl]-3-(4-hydroxy-3,5-dimethylphenyl)octanamide



C₂₉ H₃₈ N₂ O₃; Mol wt: 462.6302

ACTION – Antiatherosclerotic agent, an ACAT inhibitor (IC₅₀ = 32.4 ng/ml against enzyme from rat hepatic microsomes) shown to potently inhibit cholesterol ester formation from β -VLDL in mouse peritoneal macrophages (IC₅₀ = 14.9 ng/ml for inhibition of [¹⁴C]-oleate incorporation). In addition, compound was shown to inhibit LDL peroxidation in rat hepatic microsomes (98% inhibition at 2.5 μ g/ml). Another compound from this series of phenol derivatives is:



275073: C₂₈ H₄₀ N₂ O₃

SOURCE – Sankyo.

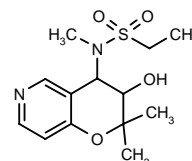
REFERENCES

1. Kogen, H. et al. (Sankyo Co., Ltd.) *Phenol derivs*. WO 9909002.

ANTIARRHYTHMIC DRUGS

272661

N-(3-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]-pyridin-4-yl)-*N*-methylethanesulfonamide



C₁₃ H₂₀ N₂ O₄ S; Mol wt: 300.3770

ACTION – Agent for the treatment of cardiovascular disorders, particularly arrhythmias, gastrointestinal ulcers and diarrhea that acts by blocking cAMP-sensitive potassium channels and which is devoid of ATP-sensitive potassium channel-opening activity. A representative compound from a series of sulfonamido-substituted pyranopyridine derivatives.

SOURCE – Hoechst Marion Roussel.

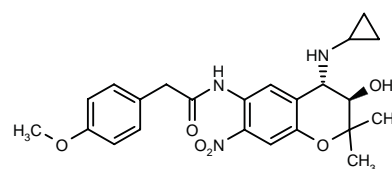
REFERENCES

1. Gerlach, U. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulphonamide-substd. pyranopyridines, process for their production and their use as a drug or diagnostics as well as medicaments containing them*. EP 895994, JP 99100382.

NIP-142

270238

N-[4(*S*)-(Cyclopropylamino)-3(*R*)-hydroxy-2,2-dimethyl-7-nitro-3,4-dihydro-2*H*-1-benzopyran-6-yl]-4-methoxybenzeneacetamide



C₂₃ H₂₇ N₃ O₆; Mol wt: 441.4813

ACTION – Antiarrhythmic agent with negative chronotropic activity, proven to inhibit L- and T-type Ca²⁺ currents in conventional whole-cell patch-clamp experiments using guinea pig ventricular cells and rabbit sinoatrial node. Compound exhibited atrium- and sinus-selective antiarrhythmic effects; its negative chronotropic activity in guinea pig right atria (> 1 μ M) was approximately 5 times that observed in right ventricular papillary muscles. Moreover, NIP-142 (10 μ M) completely inhibited aconitine-induced atrial, but not ventricular, arrhythmia and selectively prolonged the atrial, but not the ventricular, functional refractory period.

SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Chroman derivs.* JP 98087650, WO 9804542.

2. Fujikura, N. et al. *Antiarrhythmic and hemodynamic effects of a novel benzopyran derivative, NIP-142, in anesthetized animals.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-230.

3. Matsuda, T. et al. *NIP-142, a novel benzopyran derivative: Electrophysiological study on the mechanism of bradycardiac effects.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-228.

4. Ohrai, K. et al. *Structure-activity relationships and pharmacological activities of benzopyran derivatives with selective bradycardic and anti-fibrillatory effects.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-29.

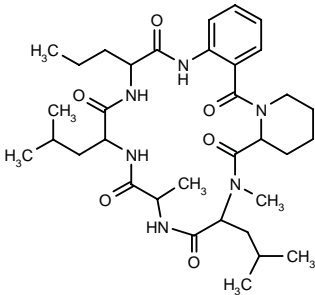
5. Yamashita, T. et al. *A novel benzopyran derivative NIP-142 has unique atrium- and sinus-selective antiarrhythmic effects in vitro.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-218.

HEART FAILURE THERAPY

PF-1171A

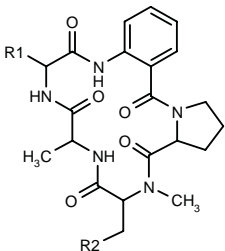
273392

10,16-Diisobutyl-13,17-dimethyl-7-propyl-5,6,7,8,9,10,11, 12,13,14,15,16,17,18,18a,19,20,21,22,24-icosahydropyrido[2,1-o][1,4,7,10,13,16]benzohexa-azacyclononadecine-6,9,12,15,18,24-hexaone

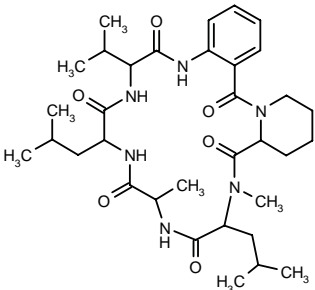


C34 H52 N6 O6; Mol wt: 640.8208

ACTION – Cardiotonic agent isolated from *Hamigera avellanea* PF 1171 (FERM P-16173), proven to increase contractile force in isolated, electrically stimulated guinea pig left atrium without affecting heart rate at a concentration of 10 µg/ml. In addition, it was shown to inhibit apolipoprotein B production in HepG2 cells (30% inhibition at 40 µg/ml). Other cyclic peptides isolated from the same source include the following:



Compound	R1	R2	Formula
PF-1171B [273393]	i-Bu	Ph	C ₃₁ H ₃₉ N ₅ O ₅
PF-1171D [273395]	i-Bu	i-Pr	C ₂₈ H ₄₁ N ₅ O ₅
PF-1171E [273396]	CH(Me)Et	i-Pr	C ₂₈ H ₄₁ N ₅ O ₅



PF-1171C [273394]: C34 H52 N6 O6

SOURCE – Meiji Seika.

REFERENCES

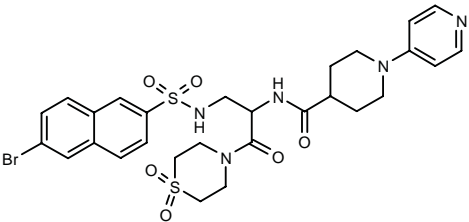
1. Magome, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cyclic peptides PF1171A, PF1171B, PF1171C, PF1171D and PF1171E and their preparation method.* JP 99021297.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

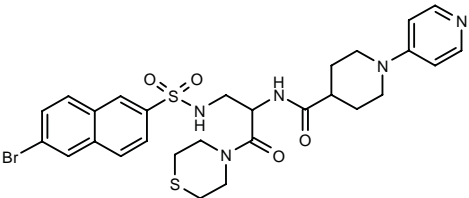
273975

N-[1-(6-Bromo-2-naphthyl)sulfonamidomethyl]-2-(1,1-dioxo-4-thiomorpholinyl)-2-oxoethyl]-1-(4-pyridinyl)-piperidine-4-carboxamide



C28 H32 Br N5 O6 S2; Mol wt: 678.6258

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of factor Xa with selectivity relative to thrombin. Another exemplified compound within this series of heteroaryl-sulfonamide derivatives is:



273977: C28 H32 Br N5 O4 S2

SOURCE – Zeneca (AstraZeneca).

REFERENCES

1. Preston, J. and Stocker, A. (Zeneca Ltd.) *(Hetero)aryl-sulfonamide derivs., their preparation and their use as factor Xa inhibitors.* WO 9909027.

SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Chroman derivs.* JP 98087650, WO 9804542.

2. Fujikura, N. et al. *Antiarrhythmic and hemodynamic effects of a novel benzopyran derivative, NIP-142, in anesthetized animals.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-230.

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4. Ohrai, K. et al. *Structure-activity relationships and pharmacological activities of benzopyran derivatives with selective bradycardic and anti-fibrillatory effects.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-29.

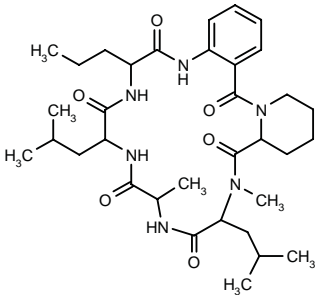
5. Yamashita, T. et al. *A novel benzopyran derivative NIP-142 has unique atrium- and sinus-selective antiarrhythmic effects in vitro.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-218.

HEART FAILURE THERAPY

PF-1171A

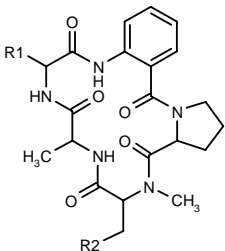
273392

10,16-Diisobutyl-13,17-dimethyl-7-propyl-5,6,7,8,9,10,11, 12,13,14,15,16,17,18,18a,19,20,21,22,24-icosahydropyrido[2,1-o][1,4,7,10,13,16]benzohexa-azacyclononadecine-6,9,12,15,18,24-hexaone

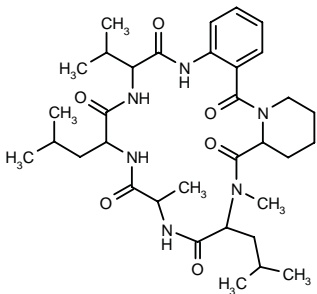


C34 H52 N6 O6; Mol wt: 640.8208

ACTION – Cardiotonic agent isolated from *Hamigera avellanea* PF 1171 (FERM P-16173), proven to increase contractile force in isolated, electrically stimulated guinea pig left atrium without affecting heart rate at a concentration of 10 µg/ml. In addition, it was shown to inhibit apolipoprotein B production in HepG2 cells (30% inhibition at 40 µg/ml). Other cyclic peptides isolated from the same source include the following:



Compound	R1	R2	Formula
PF-1171B [273393]	i-Bu	Ph	C ₃₁ H ₃₉ N ₅ O ₅
PF-1171D [273395]	i-Bu	i-Pr	C ₂₈ H ₄₁ N ₅ O ₅
PF-1171E [273396]	CH(Me)Et	i-Pr	C ₂₈ H ₄₁ N ₅ O ₅



PF-1171C [273394]: C34 H52 N6 O6

SOURCE – Meiji Seika.

REFERENCES

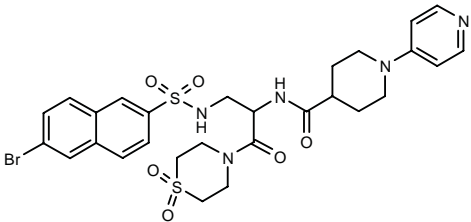
1. Magome, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cyclic peptides PF1171A, PF1171B, PF1171C, PF1171D and PF1171E and their preparation method.* JP 99021297.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

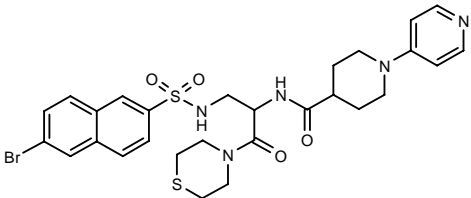
273975

N-[1-(6-Bromo-2-naphthyl)sulfonamidomethyl]-2-(1,1-dioxo-4-thiomorpholinyl)-2-oxoethyl]-1-(4-pyridinyl)-piperidine-4-carboxamide



C28 H32 Br N5 O6 S2; Mol wt: 678.6258

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of factor Xa with selectivity relative to thrombin. Another exemplified compound within this series of heteroaryl-sulfonamide derivatives is:



273977: C28 H32 Br N5 O4 S2

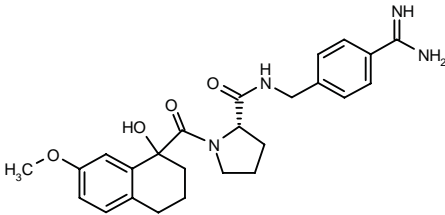
SOURCE – Zeneca (AstraZeneca).

REFERENCES

1. Preston, J. and Stocker, A. (Zeneca Ltd.) *(Hetero)aryl-sulfonamide derivs., their preparation and their use as factor Xa inhibitors.* WO 9909027.

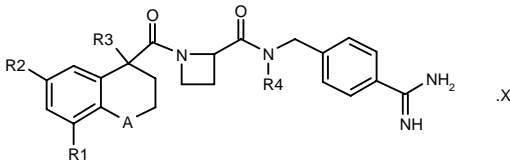
274570

N-(1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylcarbonyl-L-proline 4-amidinobenzylamide

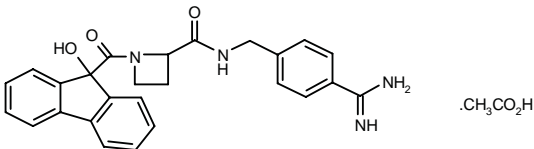


C25 H30 N4 O4; Mol wt: 450.5360

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of thrombin reported to double the thrombin clotting time of human plasma at a concentration < 0.3 μM. Other compounds from this series of amidino derivatives include the following:



Compound	R1	R2	R3	R4	A	X	Formula
274571	OMe	H	OH	H	-CH2-	acetate	C ₂₄ H ₂₈ N ₄ O ₄ .C ₂ H ₄ O ₂
274572	H	OMe	Me	H	-CH2-		C ₂₅ H ₃₀ N ₄ O ₃
274573	H	OMe	OH	H	-O-	acetate	C ₂₃ H ₂₆ N ₄ O ₅ .C ₂ H ₄ O ₂
274574	OMe	H	OH	H	bond		C ₂₃ H ₂₆ N ₄ O ₄
274575	H	Cl	OH	H	-O-	acetate	C ₂₂ H ₂₃ ClN ₄ O ₄ .C ₂ H ₄ O ₂
274576	Cl	OMe	OH	H	-O-	acetate	C ₂₃ H ₂₅ ClN ₄ O ₅ .C ₂ H ₄ O ₂
274577	H	OMe	OH	Me	-CH2-		C ₂₅ H ₃₀ N ₄ O ₄



274578: C26 H24 N4 O3 . C2 H4 O2

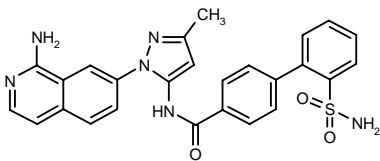
SOURCE – Astra (AstraZeneca).

REFERENCES

1. Karlsson, O. et al. (Astra AB) *New amidino derivs. and their use as thrombin inhibitors*. WO 9857932.

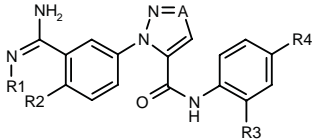
274607

N-[1-(1-Aminoisoquinolin-7-yl)-3-methylpyrazol-5-yl]-2'-sulfamoylbiphenyl-4-carboxamide

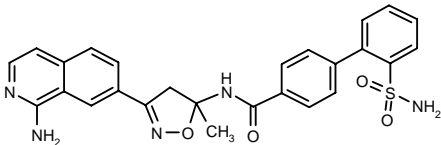


C26 H22 N6 O3 S; Mol wt: 498.5648

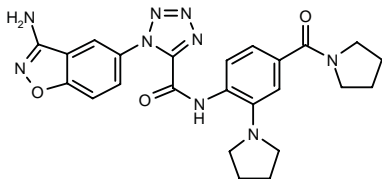
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, particularly factor Xa. Other specifically claimed compounds within this series of guanidine mimetics include the following:



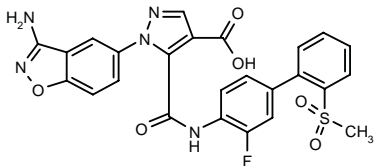
Compound	R1,R2	R3	R4	A	Formula
274610	-CH=CH-	H	2-(NH2SO2)-Ph	N	C ₂₄ H ₁₉ N ₇ O ₃ S
274611	-CH=N-	H	2-(NH2SO2)-Ph	C(Me)	C ₂₅ H ₂₁ N ₇ O ₃ S
274615	-O-	OMe	2-Me-1-imidazolyl	C(CF3)	C ₂₃ H ₁₈ F ₃ N ₇ O ₃
274622	-CH=CH-	H	2-(MeSO2)-Ph	C(Pr)	C ₂₉ H ₂₇ N ₅ O ₃ S
274624	-NH-	F	2-(NH2SO2)-Ph	C(CF3)	C ₂₄ H ₁₇ F ₄ N ₇ O ₃ S
274625	-O-	F	2-(MeNHCH2)-Ph	C(CF3)	C ₂₆ H ₂₀ F ₄ N ₆ O ₂
274626	-O-	F	2-(1-imidazolyl)-Ph	C(CF3)	C ₂₇ H ₁₇ F ₄ N ₇ O ₂



274609: C26 H23 N5 O4 S



274618: C24 H25 N9 O3



274619: C25 H18 F N5 O6 S

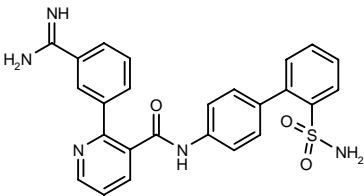
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Lam, P.Y. et al. (The Du Pont Merck Pharmaceutical Co.) *Novel guanidine mimics as factor Xa inhibitors*. WO 9857951.

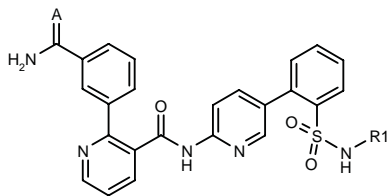
274677

2-(3-Amidinophenyl)-N-(2'-sulfamoylbiphenyl-4-yl)pyridine-3-carboxamide



C25 H21 N5 O3 S; Mol wt: 471.5389

ACTION – Anticoagulant and antithrombotic agent, a factor Xa inhibitor. Other specifically claimed compounds within this series of 6-membered aryl derivatives include the following:



Compound	R1	A	Formula
274678	H	NH	C ₂₄ H ₂₀ N ₆ O ₃ S
274680	t-Bu	NH	C ₂₈ H ₂₈ N ₆ O ₃ S
274682	H	O	C ₂₄ H ₁₉ N ₅ O ₄ S

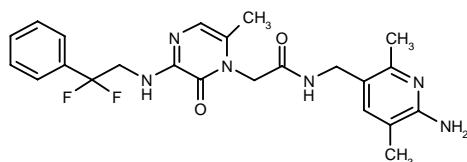
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Pruitt, J.R. et al. (The Du Pont Merck Pharmaceutical Co.) (Amidino)6-membered aromatics as factor Xa inhibitors. WO 9857934.

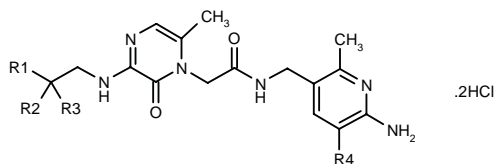
274897

N-(6-Amino-2,5-dimethyl-3-pyridylmethyl)-2-[3-(2,2-difluoro-2-phenylethylamino)-6-methyl-2-oxo-1,2-dihydro-1-pyrazinyl]acetamide



C₂₃ H₂₆ F₂ N₆ O₂; Mol wt: 456.4944

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human thrombin. Other specifically claimed compounds within this series of pyrazinone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
274899	H	H	3-F-Ph	Me	C ₂₃ H ₂₇ N ₆ O ₂ ·2HCl
274900	H	H	Ph	Me	C ₂₃ H ₂₈ N ₆ O ₂ ·2HCl
274901	F	F	cyclobutyl	H	C ₂₀ H ₂₆ F ₂ N ₆ O ₂ ·2HCl

SOURCE – Merck & Co.

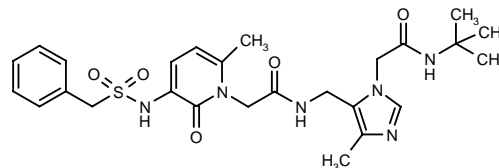
REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) Pyrazinone thrombin inhibitors. WO 9911267.

L-376062

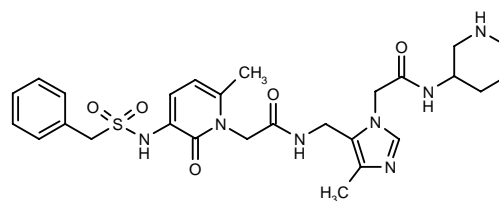
273690

3-(Benzylsulfonamido)-*N*-[1-(*N*-*tert*-butylcarbamoylmethyl)-4-methyl-1*H*-imidazol-5-ylmethyl]-6-methyl-2-oxo-1,2-dihydropyridine-1-acetamide



C₂₆ H₃₄ N₆ O₅ S; Mol wt: 542.6576

ACTION – Potent and selective, noncovalent thrombin inhibitor ($K_i = 0.36$ nM) bearing an *N*-acetamidoimidazole P₁ ligand, potentially useful for the treatment of thrombotic disorders. Another related compound is:



273691: C₂₇ H₃₅ N₇ O₅ S

SOURCE – Merck & Co.

REFERENCES

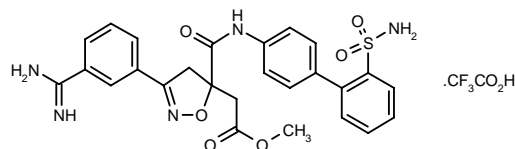
1. Isaacs, R.C.A. et al. (Merck & Co., Inc.) Thrombin inhibitors. WO 9842342.

2. Isaacs, R.C.A. et al. L-376,062. A potent, selective, noncovalent thrombin inhibitor bearing a novel imidazole P₁ ligand. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MED1 005.

SF-303

274925

(±)-2-[3-(3-Amidinophenyl)-5-[*N*-(2'-sulfamoylbiphenyl-4-yl)carbamoyl]-4,5-dihydroisoxazol-5-yl]acetic acid methyl ester trifluoroacetate



C₂₆ H₂₅ N₅ O₆ S . C₂ H F₃ O₂; Mol wt: 649.6004

ACTION – Anticoagulant and antithrombotic agent, a potent nonpeptide inhibitor of factor Xa ($K_i = 6.3$ nM for human enzyme) with high selectivity over human thrombin and trypsin ($K_i = 3100$ and 110 nM, respectively). In a rabbit model of arteriovenous shunt thrombosis, compound infused i.v. for 1 h inhibited thrombus formation with an ID₅₀ of 0.6 μmol/kg/h, without increasing the activated partial thromboplastin time (aPTT).

SOURCE – DuPont Pharmaceuticals.

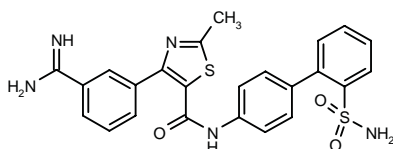
REFERENCES

1. Quan, M.L. et al. (The Du Pont Merck Pharmaceutical Co.) *Isoxazoline, isothiazoline and pyrazoline factor Xa inhibitors*. EP 874629, WO 9723212.
2. Pinto, D.J.P. et al. *Isoxazoline derivatives as potent factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, MEDI 119.
3. Quan, M.L. *Design and synthesis of isoxazoline derivatives as factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 202.
4. Wong, P.C. et al. *Nonpeptide factor Xa inhibitors. Pharmacological characterization of SF303*. FASEB J 1999, 13(4, Part 1): Abst 417.6.

SN-292

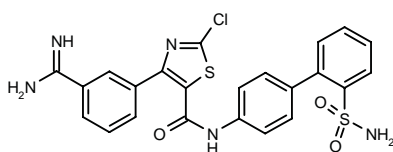
273751

4-(3-Amidinophenyl)-N-[2'-(sulfamoyl)biphenyl-4-yl]-2-methylthiazole-5-carboxamide



C24 H21 N5 O3 S2; Mol wt: 491.5939

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa ($K_i = 0.06$ nM) with excellent selectivity over thrombin and trypsin ($K_i = 1200$ and 60 nM, respectively) and good antithrombotic activity in the arteriovenous shunt thrombosis model in rabbits. another related heterocyclic carbon-linked benzamidine is:



273752: C23 H18 Cl N5 O3 S2

SOURCE – DuPont Pharmaceuticals.

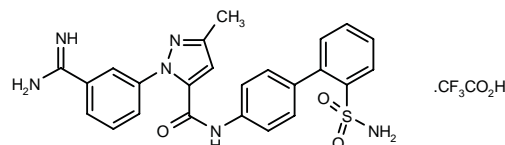
REFERENCES

1. Pruitt, J.R. et al. (The Du Pont Merck Pharmaceutical Co.) *Oxygen or sulfur containing heteroaromatics as factor Xa inhibitors*. WO 9828282.
2. Fevig, J.M. et al. *Preparation of five-membered heterocyclic carbon-linked benzamidines as highly potent inhibitors of coagulation factor Xa*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 087.

SN-429

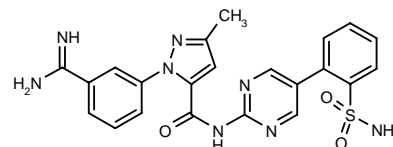
273692

1-(3-Amidinophenyl)-N-[2'-(sulfamoyl)biphenyl-4-yl]-3-methyl-1H-pyrazole-5-carboxamide trifluoroacetate



C24 H22 N6 O3 S . C2 H F3 O2; Mol wt: 588.5647

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa ($K_i = 0.01$ nM) with greater than 1000-fold selectivity over other related serine proteases ($K_i = 300$ and 16 nM for thrombin and trypsin, respectively). In the rabbit arteriovenous shunt thrombosis model, compound significantly reduced clot weight with an ED_{50} of 0.023 mg/kg/h i.v. Another related heterocyclic N-linked benzamidine compound is:



SN-116 [273693]: C22 H20 N8 O3 S

SOURCE – DuPont Pharmaceuticals.

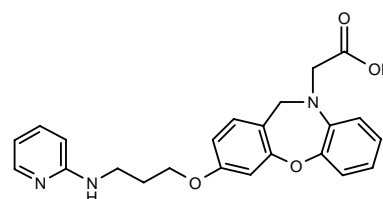
REFERENCES

1. Pinto, D.J.P. et al. (The Du Pont Merck Pharmaceutical Co.) *Nitrogen containing heteroaromatics as factor Xa inhibitors*. WO 9828269.
2. Pinto, D.J.P. et al. *Five membered heterocyclic nitrogen linked benzamidines, potent inhibitors of coagulation factor Xa*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 085.
3. Pinto, D.J.P. et al. *The discovery of a novel pyrazole SN429, a highly potent inhibitor of coagulation factor Xa*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 006.

ANTIPLATELET THERAPY

274903

2-[3-[3-(2-Pyridylamino)propoxy]-10,11-dihydrodibenzo-[b,f][1,4]oxazepin-10-yl]acetic acid



C23 H23 N3 O4; Mol wt: 405.4517

ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin) and/or fibrinogen (gpIIb/IIIa) receptor, antagonist useful for the treatment of osteoporosis, atherosclerosis, cancer and restenosis, as well as stroke, transient ischemic attacks, myocardial infarction or for inhibiting reocclusion following thrombolytic therapy.

SOURCE – SmithKline Beecham.

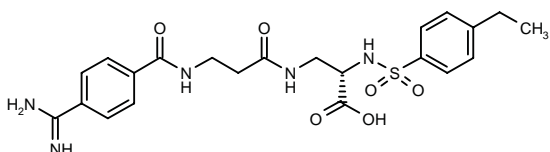
REFERENCES

1. Heerding, D.A. and Samanen, J.M. (SmithKline Beecham Corp.) *Integrin receptor antagonists*. WO 9911626.

SM-20302

259952

3-[3-(4-Amidinobenzamido)propionamido]-2(S)-(4-ethyl-phenylsulfonamido)propionic acid



C22 H27 N5 O6 S; Mol wt: 489.5503

ACTION – Potent and selective fibrinogen (gpIIb/IIIa) receptor antagonist that specifically inhibits fibrinogen binding to the gpIIb/IIIa receptor without interfering with fibronectin or vitronectin binding. Compound inhibited *ex vivo* ADP- and arachidonic acid-induced platelet aggregation in dogs with estimated IC_{50} values of 19.38 and 14.05 ng/ml, respectively, in citrated platelet-rich plasma (cPRP) and of 79.16 and 89.95 ng/ml, respectively, in heparinized PRP. Compound prevented long-term (5 days) coronary artery occlusion, reduced the incidence of myocardial infarction and improved survival in dog models of coronary artery thrombosis. Potentially useful for the prevention of arterial thrombotic events.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

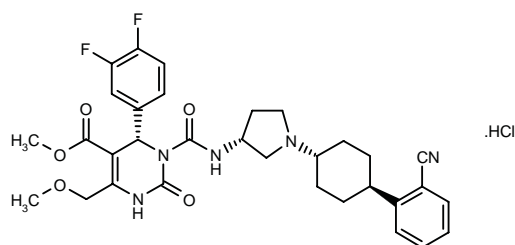
1. Ikeda, Y. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *2,3-Diaminopropionic acid deriv.* US 5707994, WO 9511228.
2. Horisawa, S. et al. *Antithrombotic effect of SM-20302, a nonpeptide GPIIb/IIIa antagonist, in a photochemically induced thrombosis model in guinea pigs.* Thromb Res 1999, 94(4): 227.
3. Huang, J.B. et al. *Temporary and partial inhibition of platelets by SM-20302 prevents coronary artery thrombosis in a chronic canine model.* Eur J Pharmacol 1999, 366(2-3): 203.
4. Rebello, S.S. et al. *In vivo efficacy of SM-20302, a GP IIb/IIIa receptor antagonist, correlates with ex vivo platelet inhibition in heparinized blood but not in citrated blood.* Arterioscler Thromb Vasc Biol 1998, 18(6): 954.
5. Rebello, S.S. et al. *Pharmacokinetics and pharmacodynamics of SM-20302, a GPIIb/IIIa receptor antagonist, in anesthetized dogs.* J Cardiovasc Pharmacol 1998, 32(3): 485.
6. Sakurama, T. et al. *SM-20302, a novel GPIIb/IIIa antagonist, has shown a selective antithrombotic activity without increasing the risk of hemorrhage in vivo.* Thromb Haemost 1997, Suppl.: Abst OC-23.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

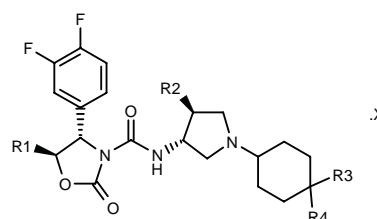
274211

3-[N-[1-[*trans*-4-(2-Cyanophenyl)cyclohexyl]pyrrolidin-3(*R*)-yl]carbamoyl]-4(*S*)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride



C32 H35 F2 N5 O5 . HCl; Mol wt: 644.1154

ACTION – Agent for the treatment of benign prostatic hyperplasia that acts as a selective antagonist at α_{1a} -adrenoceptors, being at least 10-fold less active against α_{1b} - and α_{1d} -adrenoceptors. It is reported to have reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope and lethargy compared to nonselective α_1 -adrenoceptor antagonists. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	R3	R4	X	Isomer	Formula
274214	H	H	2-CO2Et- -Ph	H	HCl	trans	C ₂₉ H ₃₃ F ₂ N ₃ O ₅ .HCl
274219	H	H	2-Pyr	OH	2HCl	cis	C ₂₅ H ₂₈ F ₂ N ₄ O ₄ .2HCl
274222	H	H	4-F- -2-MeO-Ph	H	HCl		C ₂₇ H ₃₀ F ₃ N ₃ O ₄ .HCl
274227	cyclo- propyl	H	4-CN-Ph	H	HCl		C ₃₀ H ₃₂ F ₂ N ₄ O ₃ .HCl
274228	CH2OH	H	4-F-Ph	H		trans	C ₂₇ H ₃₀ F ₃ N ₃ O ₄
274230	CONH2	H	4-F-Ph	H		trans	C ₂₇ H ₂₉ F ₃ N ₄ O ₄
274239	H	OH	2-Pyr	H		trans	C ₂₅ H ₂₈ F ₂ N ₄ O ₄

ACTION – Integrin, particularly $\alpha_v\beta_3$ (vitronectin) and/or fibrinogen (gpIIb/IIIa) receptor, antagonist useful for the treatment of osteoporosis, atherosclerosis, cancer and restenosis, as well as stroke, transient ischemic attacks, myocardial infarction or for inhibiting reocclusion following thrombolytic therapy.

SOURCE – SmithKline Beecham.

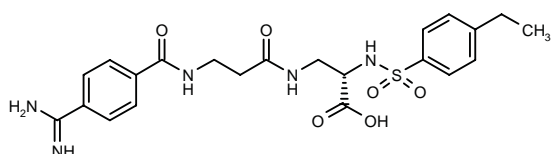
REFERENCES

1. Heerding, D.A. and Samanen, J.M. (SmithKline Beecham Corp.) *Integrin receptor antagonists*. WO 9911626.

SM-20302

259952

3-[3-(4-Amidinobenzamido)propionamido]-2(*S*)-(4-ethyl-phenylsulfonamido)propionic acid



C22 H27 N5 O6 S; Mol wt: 489.5503

ACTION – Potent and selective fibrinogen (gpIIb/IIIa) receptor antagonist that specifically inhibits fibrinogen binding to the gpIIb/IIIa receptor without interfering with fibronectin or vitronectin binding. Compound inhibited *ex vivo* ADP- and arachidonic acid-induced platelet aggregation in dogs with estimated IC_{50} values of 19.38 and 14.05 ng/ml, respectively, in citrated platelet-rich plasma (cPRP) and of 79.16 and 89.95 ng/ml, respectively, in heparinized PRP. Compound prevented long-term (5 days) coronary artery occlusion, reduced the incidence of myocardial infarction and improved survival in dog models of coronary artery thrombosis. Potentially useful for the prevention of arterial thrombotic events.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

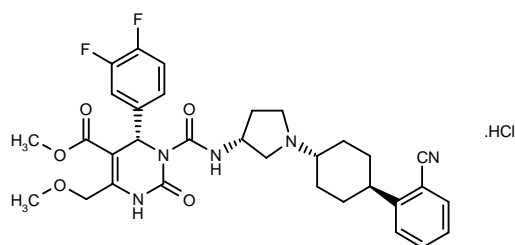
1. Ikeda, Y. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *2,3-Diaminopropionic acid deriv.* US 5707994, WO 9511228.
2. Horisawa, S. et al. *Antithrombotic effect of SM-20302, a nonpeptide GPIIb/IIIa antagonist, in a photochemically induced thrombosis model in guinea pigs.* Thromb Res 1999, 94(4): 227.
3. Huang, J.B. et al. *Temporary and partial inhibition of platelets by SM-20302 prevents coronary artery thrombosis in a chronic canine model.* Eur J Pharmacol 1999, 366(2-3): 203.
4. Rebello, S.S. et al. *In vivo efficacy of SM-20302, a GP IIb/IIIa receptor antagonist, correlates with ex vivo platelet inhibition in heparinized blood but not in citrated blood.* Arterioscler Thromb Vasc Biol 1998, 18(6): 954.
5. Rebello, S.S. et al. *Pharmacokinetics and pharmacodynamics of SM-20302, a GPIIb/IIIa receptor antagonist, in anesthetized dogs.* J Cardiovasc Pharmacol 1998, 32(3): 485.
6. Sakurama, T. et al. *SM-20302, a novel GPIIb/IIIa antagonist, has shown a selective antithrombotic activity without increasing the risk of hemorrhage in vivo.* Thromb Haemost 1997, Suppl.: Abst OC-23.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

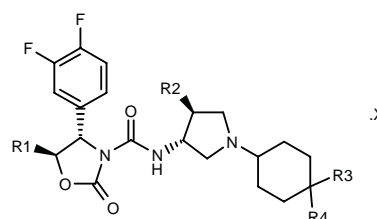
274211

3-[*N*-[1-[*trans*-4-(2-Cyanophenyl)cyclohexyl]pyrrolidin-3(*R*)-yl]carbamoyl]-4(*S*)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride

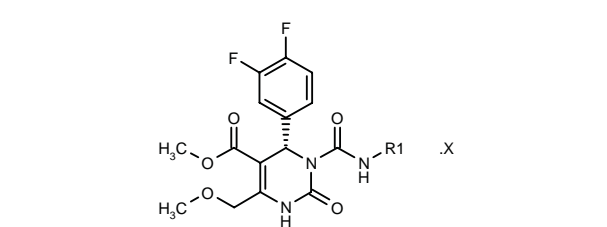


C32 H35 F2 N5 O5 . HCl; Mol wt: 644.1154

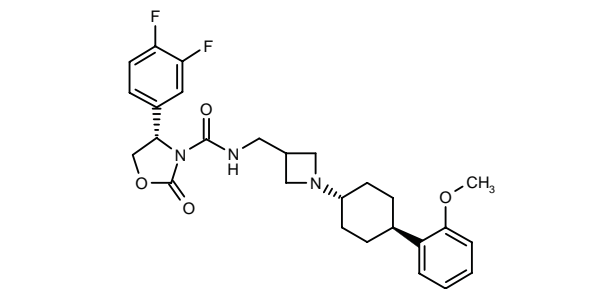
ACTION – Agent for the treatment of benign prostatic hyperplasia that acts as a selective antagonist at α_{1a} -adrenoceptors, being at least 10-fold less active against α_{1b} - and α_{1d} -adrenoceptors. It is reported to have reduced side effects related to peripheral adrenergic blockade such as hypotension, syncope and lethargy compared to nonselective α_1 -adrenoceptor antagonists. Within this series of specifically claimed compounds, the following are also included:



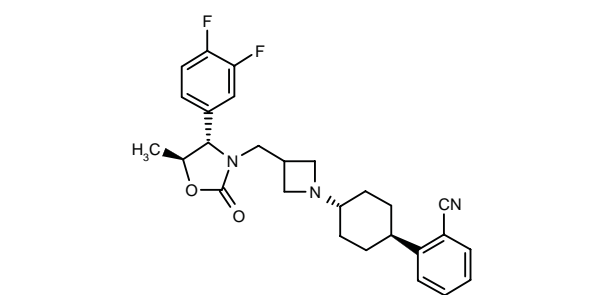
Compound	R1	R2	R3	R4	X	Isomer	Formula
274214	H	H	2-CO2Et- -Ph	H	HCl	trans	C ₂₉ H ₃₃ F ₂ N ₃ O ₅ .HCl
274219	H	H	2-Pyr	OH	2HCl	cis	C ₂₅ H ₂₈ F ₂ N ₄ O ₄ .2HCl
274222	H	H	4-F- -2-MeO-Ph	H	HCl		C ₂₇ H ₃₀ F ₃ N ₃ O ₄ .HCl
274227	cyclo- propyl	H	4-CN-Ph	H	HCl		C ₃₀ H ₃₂ F ₂ N ₄ O ₃ .HCl
274228	CH2OH	H	4-F-Ph	H		trans	C ₂₇ H ₃₀ F ₃ N ₃ O ₄
274230	CONH2	H	4-F-Ph	H		trans	C ₂₇ H ₂₉ F ₃ N ₄ O ₄
274239	H	OH	2-Pyr	H		trans	C ₂₅ H ₂₈ F ₂ N ₄ O ₄



Compound	R1	X	Formula
274218	trans-1-[4-(2-MeO-Ph)-cyclohexyl]-3(R)-pyrrolidinyl	HCl	C ₃₂ H ₃₈ F ₂ N ₄ O ₆ .HCl
274224	1-[4-OH-4-(4-F-Ph)-cyclohexyl]-3(R)-pyrrolidinyl	HCl	C ₃₁ H ₃₅ F ₃ N ₄ O ₆ .HCl
274231	trans-1-[4-(2-MeO-Ph)-cyclohexyl]-3-azetidiny-CH ₂		C ₃₂ H ₃₈ F ₂ N ₄ O ₆
274235	trans-1-[4-(2-CN-Ph)-cyclohexyl]-3-azetidiny		C ₃₁ H ₃₃ F ₂ N ₅ O ₅
274241	(trans,trans)-4-OH-1-[4-(2-Pyr)-cyclohexyl]-3-pyrrolidinyl		C ₃₀ H ₃₅ F ₂ N ₅ O ₆



274232: C27 H31 F2 N3 O4



274244: C27 H29 F2 N3 O2

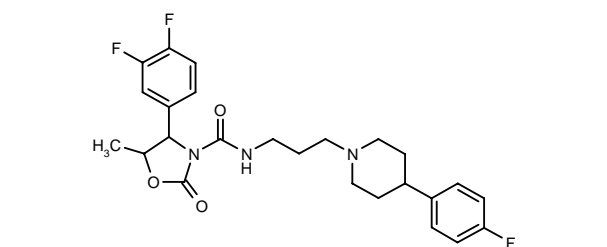
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. et al. (Merck & Co., Inc.) *alpha 1a Adrenergic receptor antagonists*. WO 9857641.

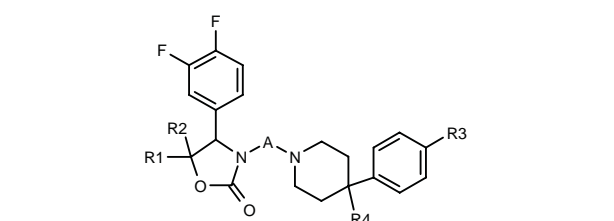
274579

4-(3,4-Difluorophenyl)-N-[3-[4-(4-fluorophenyl)piperidin-1-yl]propyl]-5-methyl-2-oxooxazolidine-3-carboxamide

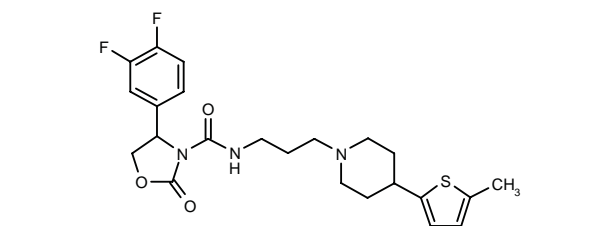


C25 H28 F3 N3 O3; Mol wt: 475.5082

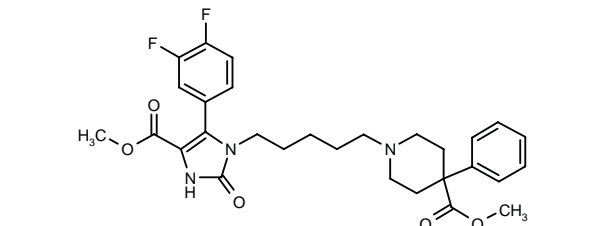
ACTION – Selective human α_{1A} -adrenoceptor antagonist reported to exhibit at least 10-fold greater affinity for the human α_{1A} -adrenoceptor than the human α_{1B} - or α_{1D} -adrenoceptor, with potential for the treatment of benign prostatic hyperplasia, impotence, pain and cardiac arrhythmia, as well as for lowering intraocular pressure and inhibiting cholesterol synthesis. Other compounds from this series of substituted piperidine derivatives include the following:



Compound	R1=R2	R3	R4	A	Formula
274581	H	F	4-F-Ph	-CONH(CH ₂) ₃ -	C ₃₀ H ₂₉ F ₄ N ₃ O ₃
274582	H	F	CN	-(E)-CH ₂ CH=CHCH ₂ CH ₂ -	C ₂₈ H ₂₆ F ₃ N ₃ O ₂
274583	Me	H	CN	-CONHCH ₂ CH(F)CH ₂ -	C ₂₇ H ₂₉ F ₃ N ₄ O ₃
274585	H	H	CO ₂ Me	-CONHCH ₂ CH ₂ -	C ₂₅ H ₂₇ F ₂ N ₃ O ₅
274586	Me	H	CN	-CONHCH ₂ CH(OH)CH ₂ -	C ₂₇ H ₃₀ F ₂ N ₄ O ₄



274580: C23 H27 F2 N3 O3 S



274584: C29 H33 F2 N3 O5

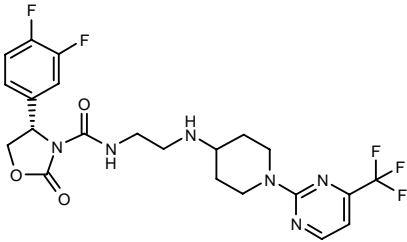
SOURCE – Synaptic.

REFERENCES

1. Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Heterocyclic subst. piperidines and uses thereof*. WO 9857940.

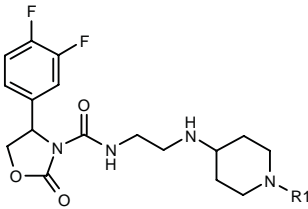
274643

4(S)-(3,4-Difluorophenyl)-2-oxo-N-[2-[1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-ylamino]ethyl]-oxazolidine-3-carboxamide

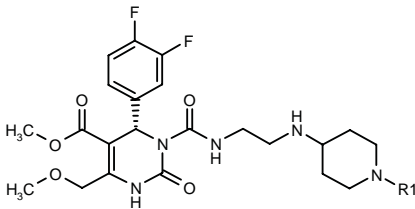


C22 H23 F5 N6 O3; Mol wt: 514.4527

ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a human α_{1a} -adrenoceptor antagonist reported to possess at least 10-fold lower affinity for human α_{1b} - and α_{1d} -adrenoceptors and many other G-protein-coupled receptors; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. Other specifically claimed compounds from this series of 1,4-disubstituted piperidine derivatives include the following:



Compound	R1	Isomer	Formula
274644	2-thiazolyl	S	C ₂₀ H ₂₃ F ₂ N ₅ O ₃ S
274645	5-CF ₃ -2-Pyr	S	C ₂₃ H ₂₄ F ₅ N ₅ O ₃
274647	2-(CF ₃ CH ₂ O)-Ph		C ₂₅ H ₂₇ F ₃ N ₄ O ₄
274648	2-(CO ₂ Me)-4-F-Ph		C ₂₅ H ₂₇ F ₃ N ₄ O ₅
274649	2-CN-4-F-Ph	S	C ₂₄ H ₂₄ F ₃ N ₅ O ₃
274650	2-NO ₂ -Ph	S	C ₂₃ H ₂₅ F ₂ N ₅ O ₅



Compound	R1	Formula
274651	2-thiazolyl	C ₂₅ H ₃₀ F ₂ N ₆ O ₅ S
274652	3-CF ₃ -2-Pyr	C ₂₆ H ₃₁ F ₅ N ₆ O ₅
274653	2-CN-Ph	C ₂₆ H ₃₂ F ₂ N ₆ O ₅
274654	2-CN-4-CF ₃ -Ph	C ₃₀ H ₃₁ F ₅ N ₆ O ₅
274655	2-CF ₃ -Ph	C ₂₉ H ₃₂ F ₅ N ₅ O ₅
274656	2-CN-5-F-Ph	C ₂₉ H ₃₁ F ₃ N ₆ O ₅

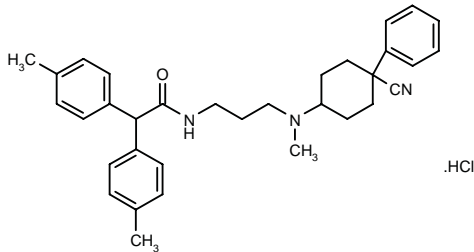
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. et al. (Merck & Co., Inc.) α_{1a} -Adrenergic receptor antagonists. WO 9857638.

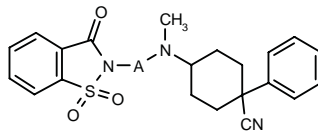
274659

N-[3-[N-(4-Cyano-4-phenylcyclohexyl)-N-methyl-amino]propyl]-2,2-bis(4-methylphenyl)acetamide hydrochloride

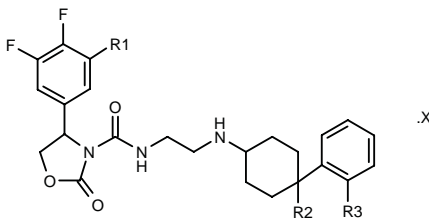


C33 H39 N3 O . HCl; Mol wt: 530.1520

ACTION – Agent for the treatment of urinary tract obstruction associated with benign prostatic hyperplasia, a human α_{1a} -adrenoceptor antagonist reported to possess at least 10-fold lower affinity for human α_{1b} -, α_{1d} -, α_{2a} -, α_{2b} - and α_{2c} -adrenoceptors; by virtue of its selectivity, compound is expected to produce fewer peripheral side effects such as hypotension, syncope and lethargy than nonselective α_1 -adrenoceptor antagonists. Other specifically claimed compounds from this series of 1,4-disubstituted cyclohexyl derivatives include the following:



Compound	A	Formula
274660	-(CH ₂) ₄ -	C ₂₆ H ₂₉ N ₃ O ₃ S
274661	-(CH ₂) ₃ -	C ₂₄ H ₂₇ N ₃ O ₃ S



Compound	R1	R2	R3	X	Isomer	Formula
274662	F	CN	H		(+)	C ₂₅ H ₂₅ F ₃ N ₄ O ₃
274663	H	CO ₂ Me	H		(+)	C ₂₆ H ₂₈ F ₂ N ₅ O ₅
274664	H	CN	OE _t			C ₂₇ H ₃₀ F ₂ N ₄ O ₄
274665	H	CN	OMe			C ₂₆ H ₂₈ F ₂ N ₄ O ₄
274666	H	CN	F			C ₂₅ H ₂₅ F ₃ N ₄ O ₃
274667	H	CN	OCF ₃			C ₂₆ H ₂₅ F ₅ N ₄ O ₄
274668	H	CN	CF ₃			C ₂₆ H ₂₅ F ₃ N ₄ O ₃
274669	H	SO ₂ Me	H	HCl		C ₂₆ H ₂₉ F ₂ N ₅ O ₅ .HCl

SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Patane, M.A. et al. (Merck & Co., Inc.; Synaptic Pharmaceutical Corp.) α_{1A} -Adrenergic receptor antagonists. WO 9857632.

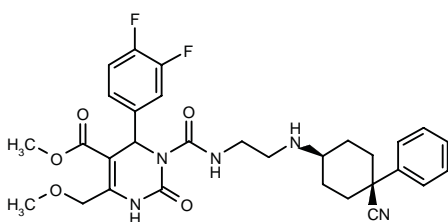
L-780945*

274081

252760 (as racemic hydrochloride)

(+)-3-[N-[2-[N-(*cis*-4-Cyano-4-phenylcyclohexyl)-amino]ethyl]carbamoyl]-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid methyl ester

(+)-SNAP-6991



C30 H33 F2 N5 O5; Mol wt: 581.6167

ACTION – Potent α_{1A} -adrenoceptor antagonist ($K_i = 0.1$ nM) with more than 130-fold selectivity over α_{1B} - and α_{1D} -adrenoceptor subtypes. *In vitro*, compound antagonized contractions induced by the α_{1A} -adrenoceptor agonist A-61603 in isolated human prostate tissue ($K_b = 0.6$ -1.4 nM), but was inactive (up to 3 μ M) against norepinephrine-induced contractions in rat and dog aorta. In anesthetized dogs, compound strongly inhibited the increase in intraurethral pressure induced by phenylephrine ($K_b = 6.4$ μ g/kg) and was much less potent in antagonizing the phenylephrine effect on diastolic blood pressure ($K_b = 116$ μ g/kg). Oral bioavailability and plasma half-life in dogs were 43% and 6.7 h, respectively. Potentially useful for ameliorating urethral obstruction caused by benign prostatic hyperplasia (BPH).

SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Nagarathnam, D. et al. (Merck & Co., Inc.; Synaptic Pharmaceutical Corp.) Dihydropyrimidines and uses thereof. EP 866708, WO 9717969.
2. Broten, T. et al. *In vivo* pharmacology of SNAP 6991 (L-780,945), an α_{1A} -selective adrenergic receptor antagonist. FASEB J 1999, 13(4, Part 1): Abst 150.7.
3. Chen, T.B. et al. *In vitro* pharmacology of SNAP 6991: An α_{1A} -adrenergic selective antagonist. FASEB J 1999, 13(4, Part 1): Abst 150.3.
4. Nagarathnam, D. et al. Design, synthesis and evaluation of dihydropyrimidinones as α_{1A} selective antagonists: 7. Modification of the piperidine moiety into 4-aminocyclohexane; identification and structure-activity relationship of SNAP 6991 analogs. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abstr MEDI 110.

*Identified compound **252760** (see **252359**) Drug Data Report 1997, 019(09): 0808.

NAFTOPIDIL*

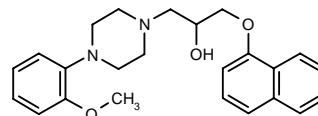
Rec INN

105012

(\pm)-1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-(1-naphthyl-oxy)-2-propanol

BM-15275

KT-611



C24 H28 N2 O3; Mol wt: 392.5020

ACTION – Selective α_1 -adrenoceptor antagonist.

INDICATION – Treatment of dysuria associated with benign prostatic hypertrophy (BPH).

PRESENTATION – Tablets, 25 and 50 mg.

PROPRIETARY NAME – Flivas (JP).

SOURCES – Asahi Chemical; licensed from Roche.

RECENT REFERENCES

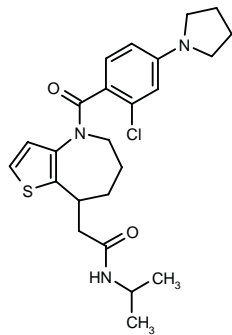
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 2. Harada, K. et al. Cardiohemodynamic effects of naftopidil in anesthetized and unanesthetized beagle dogs. Jpn Pharmacol Ther 1996, 24(6): 43.
 3. Ikegaki, I. et al. Effect of naftopidil, a novel α_1 antagonist, on phenylephrine-induced increases in prostatic and blood pressure in anesthetized dogs. Jpn J Pharmacol 1999, 79(Suppl. 1): Abstr P-594.
 4. Nishimura, N. et al. Antihypertensive effect of naftopidil, a novel α_1 -adrenoceptor antagonist, in renal hypertensive dogs. Jpn Pharmacol Ther 1996, 24(8): 123.
 5. Ohki, E. et al. Metabolic fate of naftopidil (1st report) - Absorption, distribution and excretion after single oral administration to rats and dogs. Clin Rep 1996, 30(10): 93.
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 8. Pescalli, N. et al. Effects of naftopidil on some urodynamic parameters and arterial blood pressure in comparison with prazosin in conscious rats. Pharm Res 1996, 34(3-4): 121.
 9. Takei, R. et al. Naftopidil, a novel α_1 -adrenoceptor antagonist, displays selective inhibition of canine prostatic pressure and high affinity binding to cloned human α_1 -adrenoceptors. Jpn J Pharmacol 1999, 79(4): 447.
 10. Watano, T. et al. Hypotensive effects of naftopidil in spontaneously hypertensive rats and DOCA-salt hypertensive rats. Jpn Pharmacol Ther 1996, 24(8): 113.
 11. Yamaguchi, O. et al. Dose-dependent effects and clinical usefulness of naftopidil (KT-611) on urinary obstruction caused by benign prostatic hyperplasia - Double-blind comparative study compared with placebo. Clin Rep 1997, 31(3): 373.
 12. Yamaguchi, T. et al. The effects of naftopidil on blood pressure, heart rate and plasma norepinephrine level in freely moving rabbits. Jpn Pharmacol Ther 1996, 24(6): 49.
 13. Asahi Chemical launches α -adrenoceptor antagonist in Japan. DailyDrugNews.com (Daily Essentials) 1999, March 26.
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- MONOGRAPH** – Naftopidil. Drugs Fut 1987, 12(1): 31.

*Drug Data Rep 1991, 013(10):0868.

TREATMENT OF URINARY
INCONTINENCE

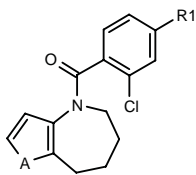
272797

2-[4-[2-Chloro-4-(1-pyrrolidinyl)benzoyl]-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepin-8-yl]-*N*-isopropylacetamide

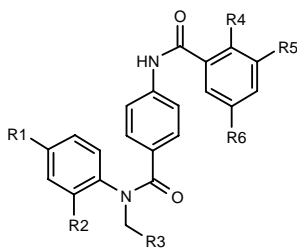


C24 H30 Cl N3 O2 S; Mol wt: 460.0390

ACTION – Vasopressin V₂ receptor agonist, as demonstrated in HeLa cells transfected with the human V₂ receptor. Potentially useful in the treatment of diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence, among other disorders. A representative compound from a series of amido derivatives, wherein the following are also included:



Compound	R1	A	Formula
272799	1-pyrrolidinyl	-O-	C ₁₉ H ₂₁ ClN ₂ O ₂
272803	NHPr	-N(Me)-	C ₁₉ H ₂₄ ClN ₃ O



Compound	R1	R2	R3	R4	R5=R6	Formula
272804	Me	2-Pyr-CH2CH2-NHCO(CH2)5O	vinyl	Me	H	C ₃₈ H ₄₂ N ₄ O ₄
272806	H	H	Me	H	Cl	C ₂₂ H ₁₈ Cl ₂ N ₂ O ₂
272807	Cl	H	Ph	Me	H	C ₂₈ H ₂₃ ClN ₂ O ₂

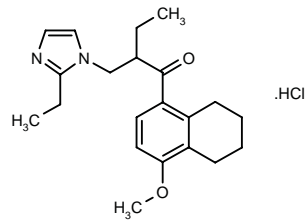
SOURCE – Otsuka.

REFERENCES

1. Kondo, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Amido derivs.* JP 99001456.

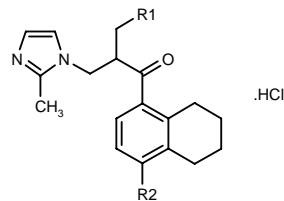
273430

2-(2-Ethyl-1*H*-imidazol-1-ylmethyl)-1-(4-methoxy-5,6,7,8-tetrahydro-1-naphthalenyl)-1-butanone hydrochloride



C21 H28 N2 O2 . HCl; Mol wt: 376.9251

ACTION – Agent for the treatment of urinary incontinence proven to decrease the frequency of rhythmic bladder contractions in rats at 5 mg/kg i.v. A representative compound from a series of aromatic ketone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
273431	H	OMe	C ₁₉ H ₂₄ N ₂ O ₂ .HCl
273432	Me	CF3	C ₂₀ H ₂₃ F ₃ N ₂ O.HCl

Compounds of the invention act as calcium antagonists in rat bladder smooth muscle.

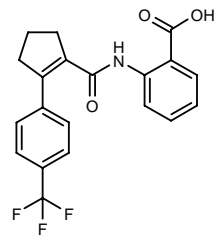
SOURCE – Nippon Kayaku.

REFERENCES

1. Koga, I. et al. (Nippon Kayaku Co., Ltd.) *Aromatic ketone derivs. and uses thereof.* WO 9903835.

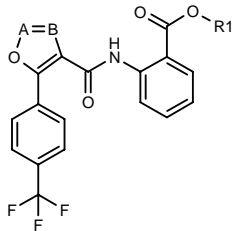
273643

2-[2-[4-(Trifluoromethyl)phenyl]-1-cyclopenten-1-ylcarboxamido]benzoic acid



C20 H16 F3 N O3; Mol wt: 375.3444

ACTION – Agent for the treatment of disorders associated with smooth muscle contraction such as urinary incontinence, irritable bowel syndrome, asthma, preterm labor, congestive heart failure, angina and cerebrovascular disease, a potent smooth muscle relaxant that acts via modulation of potassium and/or chloride channels. *In vitro*, compound was found to inhibit KCl-induced contractions of isolated rat bladder strips with an IC₅₀ value of 11.04 ± 4.04 μM. Other specifically claimed compounds include the following:



Compound	R1	A	B	Formula
273644	H	CH	N	C ₁₈ H ₁₁ F ₃ N ₂ O ₄
273645	Li	CH	N	C ₁₈ H ₁₀ F ₃ LiN ₂ O ₄
273646	H	N	C(Me)	C ₁₉ H ₁₃ F ₃ N ₂ O ₄

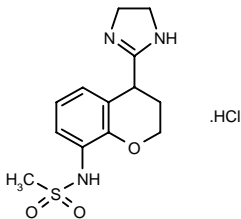
SOURCE – American Home Products.

REFERENCES

1. Lennox, J.R. et al. (American Home Products Corp.) *Anthranilic acid analogs*. WO 9907670.

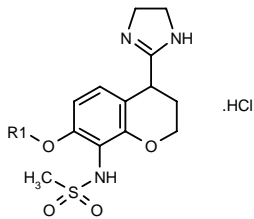
275079

N-[4-(4,5-Dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1-benzopyran-8-yl]methanesulfonamide hydrochloride



C13 H17 N3 O3 S . HCl; Mol wt: 331.8222

ACTION – Agent for the treatment of urinary incontinence, an α_1 -adrenoceptor agonist with selectivity for the urinary tract, as demonstrated by EC₅₀ values of 1.1 and 52 μ M for inducing contractions in rabbit urethra and dog carotid artery, respectively (EC₅₀ = 6.8 and 2.7 μ M, respectively, for phenylephrine). Uroselectivity was also observed *in vivo* in dogs following i.v. administration. Other compounds from this series of chromane derivatives include the following:



Compound	R1	Formula
275080	Me	C ₁₄ H ₁₉ N ₃ O ₄ S.HCl
275082	H	C ₁₃ H ₁₇ N ₃ O ₄ S.HCl

SOURCE – Mitsui Chemicals.

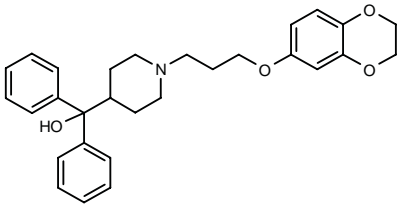
REFERENCES

1. Yamashita, H. et al. (Mitsui Chemicals, Inc.) *Novel chromane derivs. and medicines containing the same*. JP 99049771.

UFA-0272

274118

[1-[3-(2,3-Dihydro-1,4-benzodioxin-6-yloxy)propyl]-4-piperidiny](diphenyl)methanol



C29 H33 N O4; Mol wt: 459.5827

ACTION – Potent human muscarinic M₃ receptor antagonist (K_i = 2.0 nM) with some selectivity over human M₁ and M₂ receptors (K_i = 20.3 and 23.3 nM, respectively). Compound inhibited rat bladder smooth muscle contractions *in vitro* and rhythmic bladder contractions *in vivo*. Potentially useful for the treatment of urinary incontinence.

SOURCE – Taisho.

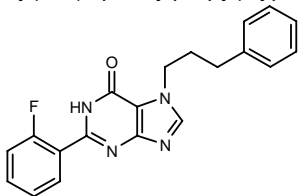
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TREATMENT OF RENAL DISEASES

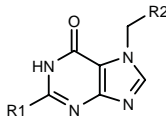
273433

2-(2-Fluorophenyl)-7-(3-phenylpropyl)hypoxanthine



C20 H17 F N4 O; Mol wt: 348.3793

ACTION – Agent for the treatment of renal diseases proven to significantly reduce proteinuria in a rat model of nephritis following oral administration of 50 mg/kg/day b.i.d. x 5 days. A representative compound from a series of purine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
273434	Et	Ph	C ₁₄ H ₁₄ N ₄ O
273436	Et	2-F-Ph	C ₁₄ H ₁₃ FN ₄ O
273437	CH ₂ NHMe	CH ₂ CH ₂ Ph	C ₁₆ H ₁₉ N ₅ O
273438	4-F-Ph	4-Me-Ph	C ₁₉ H ₁₅ FN ₄ O
273439	Pr	4-F-Ph	C ₁₅ H ₁₅ FN ₄ O

SOURCE – Japan Energy.

REFERENCES

1. Yokoyama, A. et al. (Japan Energy Corp.) *Novel purine derivs. and medicinal use thereof*. WO 9903858.

GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

ESOMEPRAZOLE

Prop INN

272598

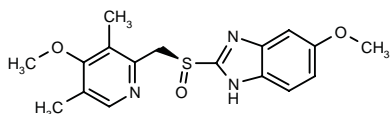
5-Methoxy-2-[(*S_s*)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole

H-199/18

(–)-Omeprazole

(*S*)-Omeprazole

Perprazole



C17 H19 N3 O3 S; Mol wt: 345.4211

ACTION – Proton pump inhibitor, the active optical isomer of omeprazole⁺ with pharmacokinetic properties that may lead to rapid resolution of symptoms and high, predictable healing rates, currently undergoing phase III clinical trials. In studies involving more than 11,000 patients with reflux esophagitis, compound (20 or 40 mg) was more effective than omeprazole (20 mg) after a short (4-week) treatment period, and its efficacy was most pronounced in patients with the most severe disease. In other studies in patients with gastroesophageal reflux disease (GERD), compound improved symptoms such as pain, reflux, burning sensation, etc. Development is initially targeted for reflux esophagitis, symptomatic GERD and *Helicobacter pylori*-associated gastric ulcer disease.

SOURCE – Astra (AstraZeneca).

REFERENCES

1. Bergstrand, P.J.A. and Lövgren, K.I. (Astra AB) *Multiple unit tableted dosage form I*. WO 9601623.

2. Bohlin, M. et al. (Astra AB) *A novel compound form*. WO 9828294.

3. Cotton, H. et al. (Astra AB) *Novel form of S-omeprazole*. WO 9854171.

4. Graham, D. et al. (Astra AB) *Enantioselective preparation of pharmaceutically active sulfoxides by bioreduction*. WO 9617077.

5. Höglberg, J.-A. et al. (Astra AB) *Process for the preparation of a magnesium salt of a substd. sulphonyl heterocycle*. WO 9741114.

6. Holt, R. et al. (Astra AB) *Enantioselective preparation of pharmaceutically active sulfoxides by biooxidation*. WO 9617076.

7. Lindberg, P.L. and Von Unge, S. (Astra AB) *Compositions*. US 5693818, US 5714504, WO 9427988.

8. Von Unge, S. (Astra AB) *A process for the optical purification of enantiomerically enriched benzimidazole derivs*. WO 9702261.

9. Balmér, K. et al. *Stereoselective effects in the separation of enantiomers of omeprazole and other substituted benzimidazoles on different chiral stationary phases*. J Chromatogr 1994, 660(1-2): 269.

10. Erlandsson, P. et al. *Resolution of the enantiomers of omeprazole and some of its analogues by liquid chromatography on a trisphenylcarbamoylcellulose-based stationary phase. The effect of the enantiomers of omeprazole on gastric glands*. J Chromatogr 1990, 532: 305.

11. Marle, I. et al. *Separation of enantiomers using cellulase (CBH I) silica as a chiral stationary phase*. J Chromatogr 1991, 586(2): 233.

12. Tanaka, M. et al. *Direct HPLC separation of enantiomers of pantoprazole and other benzimidazole sulfoxides using cellulose-based chiral stationary phases in reversed-phase mode*. Chirality 1995, 7(8): 612.

13. Tybring, G. et al. *Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects*. Clin Pharmacol Ther 1997, 62(2): 129.

14. Astra: *Interim report January-September 1998*. DailyDrugNews.com (Daily Essentials) 1998, Nov 23.

15. Astra: *Q3 and nine-month 1997 highlights*. DailyDrugNews.com (Daily Essentials) 1997, Nov 12.

16. *Major innovations fuel R&D at Astra*. DailyDrugNews.com (Daily Essentials) 1998, Jan 28.

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18. *Perprazole filings to be made within a year*. DailyDrugNews.com (Daily Essentials) 1998, Oct 13.

19. *Proposed international nonproprietary names (Prop. INN): List 79*. WHO Drug Inf 1998, 12(2): 106.

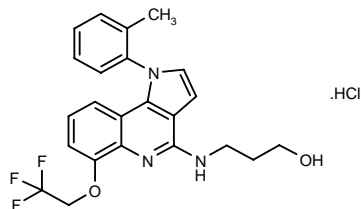
20. *Structure of Astra's next-generation proton pump inhibitor revealed for the first time*. DailyDrugNews.com (Daily Essentials) 1999, March 16.

*Drug Data Report 1988, 010(07): 0569.

ANTIULCER DRUGS

273995

3-[1-(2-Methylphenyl)-6-(2,2,2-trifluoroethoxy)-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-propanol hydrochloride



C23 H22 F3 N3 O2 . HCl; Mol wt: 465.9007

ACTION – Gastric antisecretory and antiulcer agent with a reversible gastric antisecretory effect and therefore expected to be devoid of side effects occurring upon long-term administration of irreversible inhibitors. It strongly inhibits gastric acid secretion in pylorus-ligated rats and is reported to act by inhibiting H⁺/K⁺-ATPase activity. Within this series of pyrrolo[3,2-*c*]quinoline derivatives, the following are also included:

SOURCE – Japan Energy.

REFERENCES

1. Yokoyama, A. et al. (Japan Energy Corp.) *Novel purine derivs. and medicinal use thereof*. WO 9903858.

GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

ESOMEPRAZOLE

Prop INN

272598

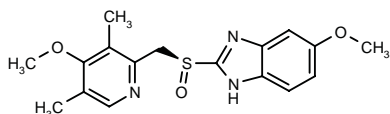
5-Methoxy-2-[(*S_s*)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole

H-199/18

(–)-Omeprazole

(*S*)-Omeprazole

Perprazole



C17 H19 N3 O3 S; Mol wt: 345.4211

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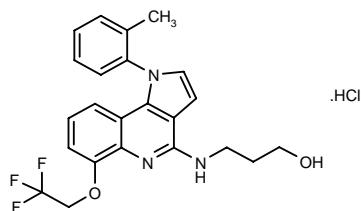
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*Drug Data Report 1988, 010(07): 0569.

ANTIULCER DRUGS

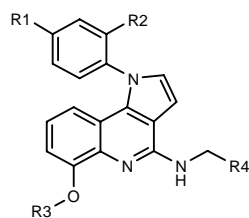
273995

3-[1-(2-Methylphenyl)-6-(2,2,2-trifluoroethoxy)-1*H*-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-propanol hydrochloride

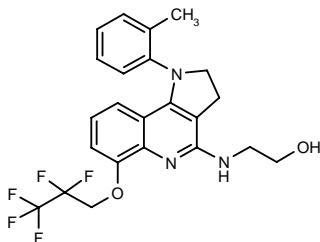


C23 H22 F3 N3 O2 . HCl; Mol wt: 465.9007

ACTION – Gastric antisecretory and antiulcer agent with a reversible gastric antisecretory effect and therefore expected to be devoid of side effects occurring upon long-term administration of irreversible inhibitors. It strongly inhibits gastric acid secretion in pylorus-ligated rats and is reported to act by inhibiting H⁺/K⁺-ATPase activity. Within this series of pyrrolo[3,2-*c*]quinoline derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
273996	H	Me	CF ₃	H	C ₂₀ H ₁₆ F ₃ N ₃ O
273997	H	Me	CF ₃	CH ₂ CH ₂ OH	C ₂₂ H ₂₀ F ₃ N ₃ O ₂
273998	H	Et	CF ₃	CH ₂ OH	C ₂₂ H ₂₀ F ₃ N ₃ O ₂
274000	H	Et	CF ₃	CH ₂ CH ₂ OH	C ₂₃ H ₂₂ F ₃ N ₃ O ₂
274001	OH	Me	CF ₃	CH ₂ OH	C ₂₁ H ₁₈ F ₃ N ₃ O ₃
274003	H	Me	CH ₂ CF ₃	CH ₂ OH	C ₂₂ H ₂₀ F ₃ N ₃ O ₂
274004	H	OMe	CH ₂ CF ₃	CH ₂ CH ₂ OH	C ₂₃ H ₂₂ F ₃ N ₃ O ₃



274005: C₂₃ H₂₂ F₅ N₃ O₂

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

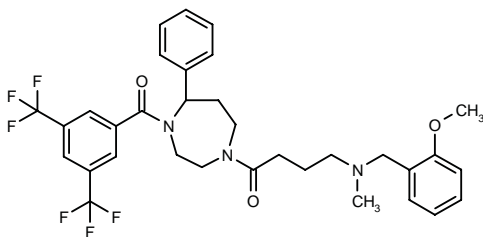
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1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *Pyrrlo[3,2-c]quinoline derivs. containing haloalkoxy group and pharmaceutically acceptable salts thereof*. WO 9909029.

AGENTS FOR IRRITABLE BOWEL SYNDROME

273931

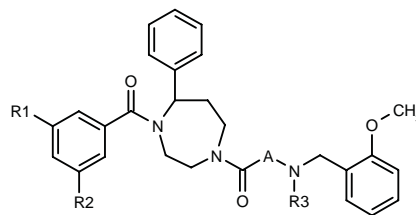
1-[4-[3,5-Bis(trifluoromethyl)benzoyl]-5-phenyl-1,4-diazepan-1-yl]-4-[*N*-(2-methoxybenzyl)-*N*-methylamino]-1-butanone



C₃₃ H₃₅ F₆ N₃ O₃; Mol wt: 635.6455

ACTION – Neurokinin NK₁ receptor antagonist (K_i = 0.012 μ M) reported to be particularly useful for the treatment of gastrointestinal disorders such as irritable bowel syndrome. Compound was shown to increase colonic transit time in rats at 21.5-100 μ mol/kg p.o. and was also found to inhibit by 39 and 61%, respectively, the number of balloon-induced colonic contractions in rats following instillation with acetic acid when given at 21.5-100

μ mol/kg s.c. Other compounds from this series of 7-phenyl-1,4-diazepan derivatives include the following:



Compound	R1=R2	R3	A	Isomer	Formula
273933	CF ₃	Me	-(CH ₂) ₃ -	(-)	C ₃₃ H ₃₅ F ₆ N ₃ O ₃
273934	Me	Me	-CH ₂ -		C ₃₁ H ₃₇ N ₃ O ₃
273935	CF ₃	H	-(CH ₂) ₃ -		C ₃₂ H ₃₃ F ₆ N ₃ O ₃

SOURCE – Solvay.

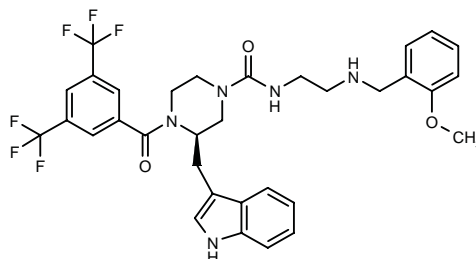
REFERENCES

1. David, S. et al. (Solvay Pharmaceuticals GmbH) *7-Phenyl-1,4-diazepane derivs. as neurokinin receptor antagonists*. EP 899264, JP 99116557.

AGENTS FOR INFLAMMATORY BOWEL DISEASE THERAPY

273929

4-[3,5-bis(Trifluoromethyl)benzoyl]-3(*R*)-(1*H*-indol-3-ylmethyl)-*N*-[2-(2-methoxybenzylamino)ethyl]piperazine-1-carboxamide



C₃₃ H₃₃ F₆ N₅ O₃; Mol wt: 661.6437

ACTION – Neurokinin receptor antagonist with high affinity for human NK₁ receptors and selectivity relative to NK₂ receptors, as demonstrated in binding assays by K_i values of 2.1 nM and 0.06 μ M, respectively. It was also found to block NK₁ receptors in a functional assay *in vitro* using isolated guinea pig aorta preparations (IC_{50} = 0.001 μ M). *In vivo*, it inhibited substance P-induced hypotension in guinea pigs with ED₅₀ values of 0.2 μ mol/kg i.v. and 0.08 μ mol/kg i.d.; when tested in the absence of substance P, compound did not produce significant changes in blood pressure at doses up to 1 μ mol/kg i.v. and 10 μ mol/kg i.d., thus showing no calcium-antagonist side effects. A specifically claimed compound within a series of indolemethyl-*N,N'*-bisacylpiperazine derivatives expected to be particularly useful in the treatment of gastrointestinal disorders such as inflammatory bowel disease (IBD).

SOURCE – Solvay.

REFERENCES

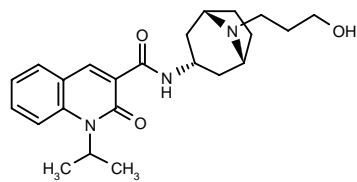
1. Jasserand, D. et al. (Solvay Pharmaceuticals GmbH) *Indolylmethyl-N,N'-bisacylpiperazines as neurokinine receptor antagonists*. EP 899270.

TREATMENT OF DISORDERS OF
GASTRIC EMPTYING

TS-951*

234689

endo-N-[8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxamide



C23 H31 N3 O3; Mol wt: 397.5220

ACTION – Potent 5-HT₄ receptor agonist (K_i = 11.5 and 3.8 nM against [³H]-GR-113808 binding in guinea pig striatum and mouse whole brain membranes, respectively) with high selectivity over other 5-HT subtype receptors (K_i > 1 μM). Compound showed agonist and partial agonist activity in isolated longitudinal muscle from guinea pig ileum (EC₅₀ = 3.19 nM) and distal colon (EC₅₀ = 20.1 nM), respectively. In conscious dogs, it dose-dependently stimulated postprandial antral and colonic motor activity, both effects being inhibited by the selective 5-HT₄ receptor antagonist SB-207266 and atropine.

SOURCE – Taisho.

REFERENCES

1. Ohuchi, Y. et al. (Taisho Pharmaceutical Co., Ltd.) *Quinolinecarboxylic acid deriv.* EP 710662, JP 96034784, US 5753673, WO 9531455.

2. Ito, C. et al. *Involvement of 5-HT₄ receptors in regulation of defecation.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-347.

3. Kajita, S. et al. *Pharmacological characterization of a novel 5-HT₄ receptor agonist, TS-951 in vitro.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-337.

4. Noguchi, K. et al. *Effects of 5-HT₄ receptor agonists on the action potential parameters of isolated rabbit myocardium.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-346.

5. Yasuda, S. et al. *Comparison of gastric antral and colonic motility mediated by 5-HT₄ receptors in conscious dogs.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-342.

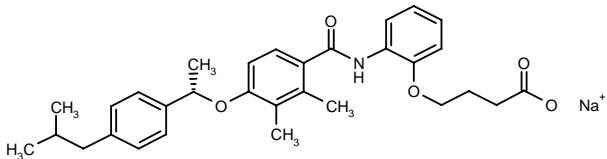
*Identified compound **234689** (see **231319**) Drug Data Report 1996, 018(05): 0438.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

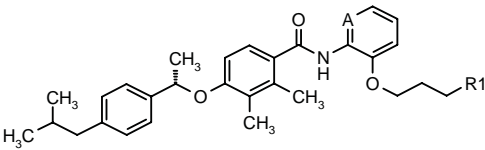
273615

4-[2-[4-[1(S)-(4-Isobutylphenyl)ethoxy]-2,3-dimethyl-benzamido]phenoxy]butyric acid sodium salt



C31 H36 N Na O5; Mol wt: 525.6174

ACTION – Peroxisome proliferator-activated receptor γ (PPARγ) agonist with comparable potency to troglitazone, proven to exert potent blood glucose-, free fatty acid- and triglyceride-lowering activity in *db/db* mice at 100 mg/kg/day p.o. x 14 days. Potentially useful for the treatment or prevention of hyperglycemia, diabetes, obesity, syndrome X, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertension, arteriosclerosis, circulatory diseases and hyperphagia. Other compounds from this series of substituted benzamide derivatives include the following:



Compound	R1	A	Formula
273616	CO2H	N	C ₃₀ H ₃₆ N ₂ O ₅
273617	5-tetrazolyl	CH	C ₃₁ H ₃₇ N ₅ O ₃

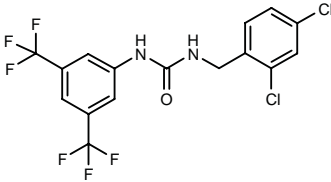
SOURCE – Ono.

REFERENCES

1. Tajima, H. et al. (Ono Pharmaceutical Co., Ltd.) *γ-Type regulators for peroxisome proliferator-activated receptor.* WO 9907357.

273633

N-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-(2,4-dichlorobenzyl)urea



C16 H10 Cl2 F6 N2 O; Mol wt: 431.1620

SOURCE – Solvay.

REFERENCES

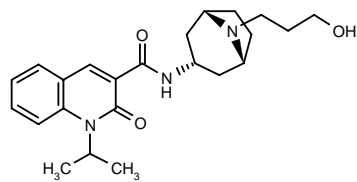
1. Jasserand, D. et al. (Solvay Pharmaceuticals GmbH) *Indolylmethyl-N,N'-bisacylpiperazines as neurokinine receptor antagonists*. EP 899270.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

TS-951*

234689

endo-N-[8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxamide



C23 H31 N3 O3; Mol wt: 397.5220

ACTION – Potent 5-HT₄ receptor agonist (K_i = 11.5 and 3.8 nM against [³H]-GR-113808 binding in guinea pig striatum and mouse whole brain membranes, respectively) with high selectivity over other 5-HT subtype receptors (K_i > 1 μM). Compound showed agonist and partial agonist activity in isolated longitudinal muscle from guinea pig ileum (EC_{50} = 3.19 nM) and distal colon (EC_{50} = 20.1 nM), respectively. In conscious dogs, it dose-dependently stimulated postprandial antral and colonic motor activity, both effects being inhibited by the selective 5-HT₄ receptor antagonist SB-207266 and atropine.

SOURCE – Taisho.

REFERENCES

1. Ohuchi, Y. et al. (Taisho Pharmaceutical Co., Ltd.) *Quinolincarboxylic acid deriv.* EP 710662, JP 96034784, US 5753673, WO 9531455.

2. Ito, C. et al. *Involvement of 5-HT₄ receptors in regulation of defecation.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-347.

3. Kajita, S. et al. *Pharmacological characterization of a novel 5-HT₄ receptor agonist, TS-951 in vitro.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-337.

4. Noguchi, K. et al. *Effects of 5-HT₄ receptor agonists on the action potential parameters of isolated rabbit myocardium.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-346.

5. Yasuda, S. et al. *Comparison of gastric antral and colonic motility mediated by 5-HT₄ receptors in conscious dogs.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-342.

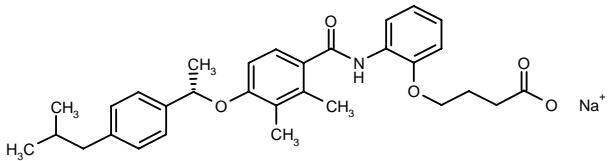
*Identified compound **234689** (see **231319**) Drug Data Report 1996, 018(05): 0438.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

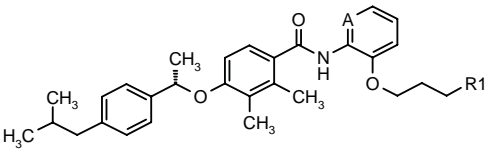
273615

4-[2-[4-[1 (S)-(4-Isobutylphenyl)ethoxy]-2,3-dimethyl-benzamido]phenoxy]butyric acid sodium salt



C31 H36 N Na O5; Mol wt: 525.6174

ACTION – Peroxisome proliferator-activated receptor γ (PPAR γ) agonist with comparable potency to troglitazone, proven to exert potent blood glucose-, free fatty acid- and triglyceride-lowering activity in *db/db* mice at 100 mg/kg/day p.o. x 14 days. Potentially useful for the treatment or prevention of hyperglycemia, diabetes, obesity, syndrome X, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertension, arteriosclerosis, circulatory diseases and hyperphagia. Other compounds from this series of substituted benzamide derivatives include the following:



Compound	R1	A	Formula
273616	CO ₂ H	N	C ₃₀ H ₃₆ N ₂ O ₅
273617	5-tetrazolyl	CH	C ₃₁ H ₃₇ N ₅ O ₃

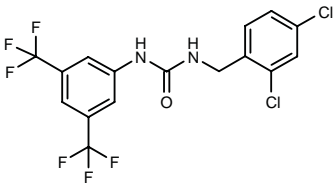
SOURCE – Ono.

REFERENCES

1. Tajima, H. et al. (Ono Pharmaceutical Co., Ltd.) *γ -Type regulators for peroxisome proliferator-activated receptor.* WO 9907357.

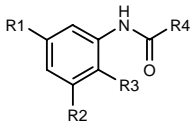
273633

N-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-(2,4-dichlorobenzyl)urea



C16 H10 Cl2 F6 N2 O; Mol wt: 431.1620

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of 2,5- and 3,5-disubstituted anilines, the following are also specifically claimed:



Compound	R1	R2	R3	R4	Formula
273634	Cl	Cl	H	cyclohexyl-CH2NH	C ₁₄ H ₁₈ Cl ₂ N ₂ O
273635	F	F	H	cyclohexyl-CH2NH	C ₁₄ H ₁₈ F ₂ N ₂ O
273636	F	H	F	cyclohexyl-CH2NH	C ₁₄ H ₁₈ F ₂ N ₂ O
273637	F	F	H	(R)-cyclohexyl-CH(Me)NH	C ₁₅ H ₂₀ F ₂ N ₂ O
273638	CF3	CF3	H	n-C6H13	C ₁₅ H ₁₇ F ₆ NO
273639	CF3	CF3	H	CH(Me)OPh	C ₁₇ H ₁₃ F ₆ NO ₂
273640	CF3	CF3	H	4-Cl-PhNH	C ₁₅ H ₉ ClF ₆ N ₂ O
273641	CF3	CF3	H	CH=CHPh	C ₁₇ H ₁₁ F ₆ NO
273642	CF3	CF3	H	2-Ph-cyclopropyl	C ₁₈ H ₁₃ F ₆ NO

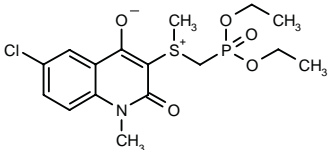
SOURCE – Novo Nordisk.

REFERENCES

1. Dorwald, F.Z. et al. (Novo Nordisk A/S) *Derivs. of 2,5- and 3,5-disubstd. anilines, their preparation and use.* WO 9907672.

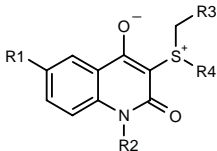
273673

6-Chloro-3-[[diethoxyphosphorylmethyl](methyl)sulfonio]-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate



C16 H21 Cl N O5 P S; Mol wt: 405.8369

ACTION – Antidiabetic agent proven to decrease blood glucose levels by 55% in dexamethasone-treated rats at a dose of 100 mg/kg/day p.o. x 4 days. Other compounds within this series of 2-oxo-1,2-dihydroquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
273674	H	Me	-CH2CH2COCH2-		C ₁₅ H ₁₅ NO ₃ S
273675	Cl	Me	H	CH2CONHMe	C ₁₄ H ₁₅ ClN ₂ O ₃ S
273676	H	Ph	H	CH2CONHMe	C ₁₉ H ₁₈ N ₂ O ₃ S
273677	Cl	Et	H	CH2PO(OEt)2	C ₁₇ H ₂₃ ClNO ₃ PS
273678	Cl	Et	H	CH2CONHMe	C ₁₅ H ₁₇ ClN ₂ O ₃ S

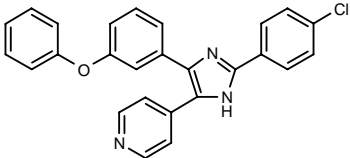
SOURCE – Otsuka.

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1. Shibuya, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Medicinal compsns. containing dihydroquinoline derivs.* JP 99029478.

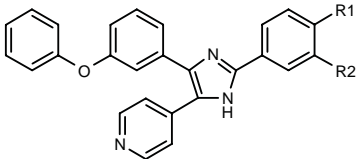
273961

4-[2-(4-Chlorophenyl)-4-(3-phenoxyphenyl)-1*H*-imidazol-5-yl]pyridine



C26 H18 Cl N3 O; Mol wt: 423.9012

ACTION – Glucagon receptor antagonist for the treatment of disease states mediated by elevated glucagon levels such as diabetes, obesity, hypertension and cachexia. Other specifically claimed compounds from this series of triaryl substituted imidazole derivatives include the following:



Compound	R1	R2	Formula
273962	H	Cl	C ₂₆ H ₁₈ ClN ₃ O
273963	Cl	Cl	C ₂₆ H ₁₇ Cl ₂ N ₃ O
273964	OPh	H	C ₃₂ H ₂₃ N ₃ O ₂
273965	CF3	H	C ₂₇ H ₁₈ F ₃ N ₃ O
273966	Br	H	C ₂₆ H ₁₈ BrN ₃ O
273967	F	H	C ₂₆ H ₁₈ FN ₃ O
273968	OCH2Ph	H	C ₃₃ H ₂₅ N ₃ O ₂

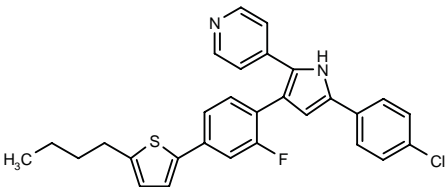
SOURCE – Merck & Co.

REFERENCES

1. Chang, L.L. (Merck & Co., Inc.) *Triaryl substd. imidazoles as glucagon antagonists.* US 5880139, WO 9822109.

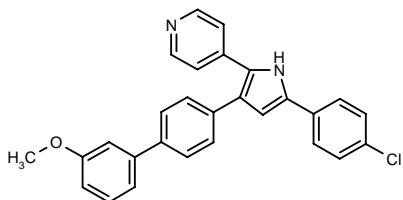
274047

4-[3-[4-(5-Butyl-2-thienyl)-2-fluorophenyl]-5-(4-chlorophenyl)-1*H*-pyrrol-2-yl]pyridine



C29 H24 Cl F N2 S; Mol wt: 487.0396

ACTION – Potent glucagon receptor antagonist ($IC_{50} = 2$ and 51 nM, respectively, against [^{125}I]-glucagon binding to human glucagon receptors expressed in CHO cells in the absence and presence of Mg^{2+}). In a functional assay in CHO cells expressing human receptors, compound inhibited glucagon-stimulated cAMP synthesis ($IC_{50} = 0.28 \mu M$). Potentially useful for the treatment of type I and type II diabetes. Another compound in this series of pyridyl-pyrroles is:



274045: C₂₈ H₂₁ Cl N₂ O

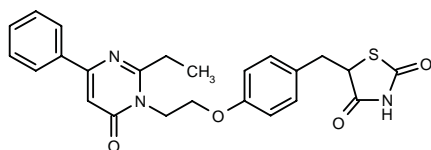
SOURCE – Merck & Co.

REFERENCES

- Chang, L.L. et al. (Merck & Co., Inc.) *Substd. pyridyl pyrroles, compsns. containing such cpds. and methods of use*. US 5776954.
- De Laszlo, S.E. et al. (Merck & Co., Inc.) *Substd. pyridyl pyrroles, compsns. containing such cpds. and methods of use*. EP 859771, WO 9716442.
- Kim, D. et al. *Design and synthesis of pyridyl pyrroles as glucagon receptor antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 067.

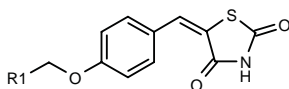
274461

5-[4-[2-[2-Ethyl-6-oxo-4-phenyl-1,6-dihydro-1-pyrimidinyl]ethoxy]benzyl]thiazolidine-2,4-dione

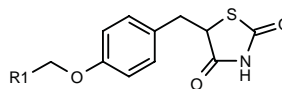


C₂₄ H₂₃ N₃ O₄ S; Mol wt: 449.5287

ACTION – Antidiabetic agent proven to decrease blood glucose and triglyceride levels in *db/db* mice by 64 and 76%, respectively, when given at 30 mg/kg/day p.o. x 6 days; in this model, troglitazone decreased glucose levels by 28% at 100 mg/kg/day p.o. x 6 days. Other compounds from this series of azolidinedione derivatives include the following:



Compound	R1	Formula
274462	2-Et-4-Me-6-oxo-1,6-dihydro-1-pyrimidinyl-CH ₂	C ₁₉ H ₁₉ N ₃ O ₄ S
274463	2,5-(Et)2-4-Me-6-oxo-1,6-dihydro-1-pyrimidinyl-CH ₂	C ₂₁ H ₂₃ N ₃ O ₄ S
274464	2-Et-4-Ph-6-oxo-1,6-dihydro-1-pyrimidinyl-CH ₂	C ₂₄ H ₂₁ N ₃ O ₄ S
274465	2-Me-4-oxo-3,4-dihydro-3-quinazolinyl-CH ₂	C ₂₁ H ₁₇ N ₃ O ₄ S
274467	3-Me-4-oxo-3,4-dihydro-2-quinazolinyl	C ₂₀ H ₁₅ N ₃ O ₄ S
274468	3-Et-4-oxo-3,4-dihydro-2-quinazolinyl	C ₂₁ H ₁₇ N ₃ O ₄ S



Compound	R1	Formula
274469	4-Me-2-Pr-6-oxo-1,6-dihydro-1-pyrimidinyl-CH ₂	C ₂₀ H ₂₃ N ₃ O ₄ S
274470	2-Et-4-Me-6-oxo-1,6-dihydro-1-pyrimidinyl-CH ₂	C ₁₉ H ₂₁ N ₃ O ₄ S
274471	3-Me-4-oxo-3,4-dihydro-2-quinazolinyl-	C ₂₀ H ₁₇ N ₃ O ₄ S
274472	2-Et-4-oxo-3,4-dihydro-3-quinazolinyl-CH ₂	C ₂₂ H ₂₁ N ₃ O ₄ S

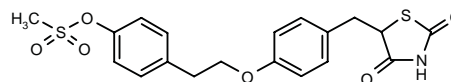
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

REFERENCES

- Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Heterocyclic cpds., process for their preparation and pharmaceutical compsns. containing them and their use in the treatment of diabetes and related diseases*. US 5885997.

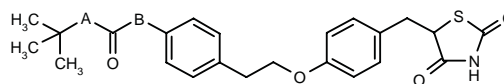
274587

5-[4-[2-[4-(Methanesulfonyloxy)phenyl]ethoxy]benzyl]thiazolidine-2,4-dione



C₁₉ H₁₉ N O₆ S₂; Mol wt: 421.4921

ACTION – Thiazolidinedione insulin sensitizer reported to be more potent than troglitazone following oral administration in *ob/ob* mice. Other specifically claimed compounds within this series of thiazolidinedione, oxazolidinedione and oxadiazolidinedione derivatives include the following:



Compound	A	B	Formula
274588	NH	O	C ₂₃ H ₂₈ N ₂ O ₅ S
274589	O	NH	C ₂₃ H ₂₈ N ₂ O ₅ S

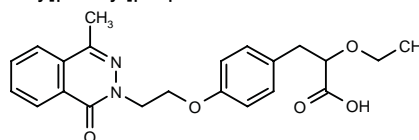
SOURCE – Astra (AstraZeneca).

REFERENCES

- Andersson, K. et al. (Astra AB) *New thiazolidinedione, oxazolidinedione and oxadiazolidinedione derivs*. WO 9857941.

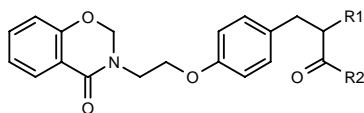
275035

2-Ethoxy-3-[4-[2-(4-methyl-1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propionic acid

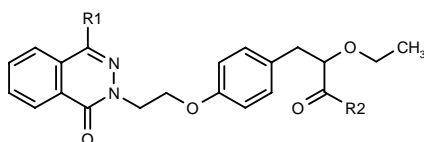


C₂₂ H₂₄ N₂ O₅; Mol wt: 396.4406

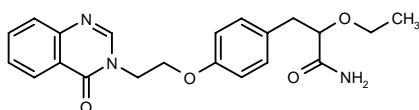
ACTION – Agent for the treatment or prevention of diabetes mellitus, hyperlipidemia and obesity proven to decrease blood glucose levels by 50% in diabetic *db/db* mice at 10 mg/kg/day p.o. x 4 days, being more potent than pioglitazone (26% reduction at 20 mg/kg/day p.o. x 4 days). Other compounds from this series of α -substituted phenylpropionic acid derivatives include the following:



Compound	R1	R2	Formula
275037	OMe	NH2	C ₂₀ H ₂₂ N ₂ O ₅
275039	NHEt	OEt	C ₂₃ H ₂₈ N ₂ O ₅
275040	NHEt	OH	C ₂₁ H ₂₄ N ₂ O ₅
275041	SEt	OH	C ₂₁ H ₂₃ NO ₅ S



Compound	R1	R2	Formula
275042	H	OH	C ₂₁ H ₂₂ N ₂ O ₅
275043	H	OEt	C ₂₃ H ₂₈ N ₂ O ₅
275044	H	NHOH	C ₂₁ H ₂₃ N ₃ O ₅
275045	Me	OEt	C ₂₄ H ₂₈ N ₂ O ₅



275036: C₂₁ H₂₃ N₃ O₄

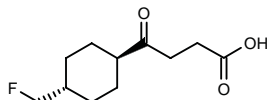
SOURCE – SS Pharmaceutical.

REFERENCES

1. Nagao, Y. et al. (SS Pharmaceutical, Ltd.) α -Substd. phenylpropionic acid deriv. and medicine containing the same. EP 903343.

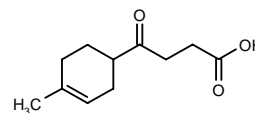
275075

trans-4-[4-(Fluoromethyl)cyclohexyl]-4-oxobutyrlic acid

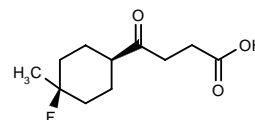


C₁₁ H₁₇ F O₃; Mol wt: 216.2503

ACTION – Antidiabetic agent, as demonstrated in fasted rats by a reduction in glycemia of 56.5 and 20.6% at 30 and 120 min after an i.p. glucose load, respectively, when given at 100 mg/kg p.o. Other compounds from this series of cyclohexyl and cyclohexenyl derivatives include the following:



275077: C₁₁ H₁₆ O₃



275078: C₁₁ H₁₇ F O₃

SOURCE – Japan Tobacco.

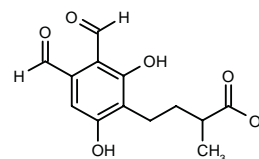
REFERENCES

1. Shinkai, H. et al. (Japan Tobacco Inc.) *Cyclic cpds. and medicinal use thereof*. WO 9908991.

HERICENAL C

274380

4-(3,4-Diformyl-2,6-dihydroxyphenyl)-2-methylbutyric acid



C₁₃ H₁₄ O₆; Mol wt: 266.2476

ACTION – Antidiabetic agent, an inhibitor of the glucose-6-phosphate translocase component of glucose-6-phosphatase (IC₅₀ = 8 μ g/ml), produced by culturing the microorganism *Hericum erinaceus* DSM 10600.

SOURCE – Hoechst Marion Roussel.

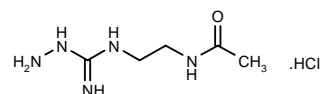
REFERENCES

1. Vértessy, L. et al. (Hoechst Marion Roussel Deutschland GmbH) *New derivs. of phthalaldehyde, process for their preparation and their use*. EP 902002.

TREATMENT OF DIABETIC COMPLICATIONS

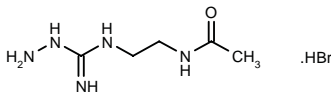
273917

N-[2-(*N*-Aminoguanidino)ethyl]acetamide hydrochloride



C₅ H₁₃ N₅ O . HCl; Mol wt: 195.6526

ACTION – Agent for the treatment of diabetic complications and aging that acts by inhibiting the formation of advanced glycosylation endproducts (AGEs), as demonstrated *in vitro* by inhibition of the crosslinking of glycated bovine serum albumin (AGE–BSA) to rat tail tendon collagen, as well as of the crosslinking of *N*-acetyl-glycyl-lysine methyl ester in the presence of ribose, with comparable potency to the known compound aminoguanidine. Contrary to aminoguanidine, compound was found to be selective, having no significant effect on the enzymes diamine oxidase or inducible nitric oxide synthase (iNOS). Another specifically claimed compound is:



273918: C₅ H₁₃ N₅ O . HBr

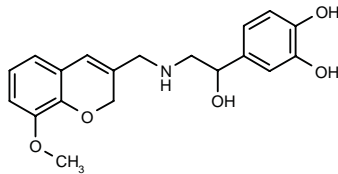
SOURCE – Alteon.

REFERENCES

1. Ulrich, P.C. and Wagle, D.R. (Alteon Inc.) *N*-Acylaminoalkyl-hydrazinecarboximidamides. US 5877217.

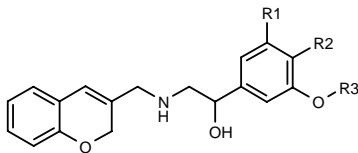
275005

4-[1-Hydroxy-2-[8-methoxy-2*H*-1-benzopyran-3-ylmethylamino]ethyl]benzene-1,2-diol



C₁₉ H₂₁ N O₅; Mol wt: 343.3769

ACTION – Agent for the treatment or prevention of diabetic complications, arteriosclerosis and aging that acts by inhibiting the formation of advanced glycosylation endproducts (AGE). Its activity was evaluated by measuring the ability to inhibit the formation of protein crosslinks (IC₅₀ = 3 µg/ml). Other exemplified compounds from this series of chromene derivatives include the following:



Compound	R1	R2	R3	Formula
275006	H	H	H	C ₁₈ H ₁₉ NO ₃
275007	OMe	OH	Me	C ₂₀ H ₂₃ NO ₅

SOURCE – SS Pharmaceutical.

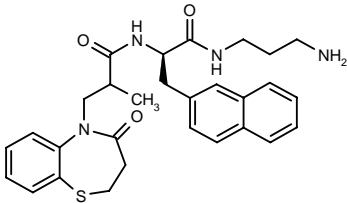
REFERENCES

1. Ishii, F. et al. (SS Pharmaceutical, Ltd.) *Chromene derivs. and salts thereof, and pharmaceuticals containing the same*. EP 906910, JP 99106381.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

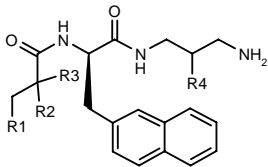
274262

N-[2-(3-Aminopropylamino)-1(*R*)-(2-naphthylmethyl)-2-oxoethyl]-2-methyl-3-(4-oxo-3,4-dihydro-2*H*-1,5-benzothiazepin-5-yl)propionamide

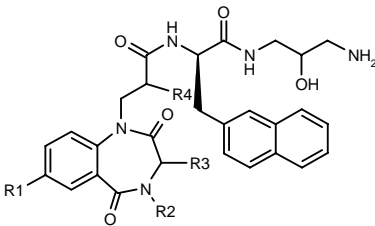


C₂₉ H₃₄ N₄ O₃ S; Mol wt: 518.6786

ACTION– Growth hormone (GH) release promoter whose activity was demonstrated *in vitro* in primary rat anterior pituitary cell preparations at a concentration below 0.01 µM. *In vivo* activity was demonstrated in rats treated with 10 mg/kg p.o. Within this series of amide derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
274263	6,11-dioxo-6,11-dihydro-5 <i>H</i> -dibenzo[<i>b,e</i>]azepin-5-yl	H	H	H	C ₃₃ H ₃₂ N ₄ O ₄
274264	4-oxo-3,4-dihydro-2 <i>H</i> -1,5-benzothiazepin-5-yl-CH ₂	Me	H	OH	C ₂₉ H ₃₄ N ₄ O ₃ S
274265	1,1,4-trioxo-3,4-dihydro-2 <i>H</i> -1,5-benzothiazepin-5-yl-CH ₂	Me	Me	OH	C ₃₀ H ₃₆ N ₄ O ₆ S



Compound	R1	R2,R3	R4	Isomer	Formula
274266	Cl	-(CH ₂) ₃ -	H	S	C ₃₁ H ₃₄ ClN ₅ O ₅
274267	H	-(CH ₂) ₃ -	Me	S	C ₃₂ H ₃₇ N ₅ O ₅
274268	H	-(CH ₂) ₄ -	H		C ₃₂ H ₃₇ N ₅ O ₅

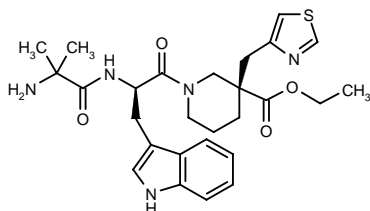
SOURCE – Kaken.

REFERENCES

1. Funamizu, H. et al. (Kaken Pharmaceutical Co., Ltd.) *Novel amide derivs*. WO 9909991.

L-165666**274054**

1-(2-Methylalanyl-D-tryptophyl)-3-(4-thiazolyl-methyl)piperidine-3(S)-carboxylic acid ethyl ester



C27 H35 N5 O4 S; Mol wt: 525.6705

ACTION – Potent, orally bioavailable growth hormone secretagogue ($EC_{50} = 0.5$ nM in a growth hormone release assay in cultured rats pituitary cells) with a short duration of action. Compound at 10 μ M did not bind to opiate, neurokinin, adrenergic, somatostatin, cholecystokinin, bradykinin, vasopressin or benzodiazepine receptors. *In vivo*, it stimulated GH secretion in dogs, with low doses of 0.0025 mg/kg i.v. and 0.25 mg/kg p.o. causing a 4-fold increase in serum GH.

SOURCE – Merck & Co.

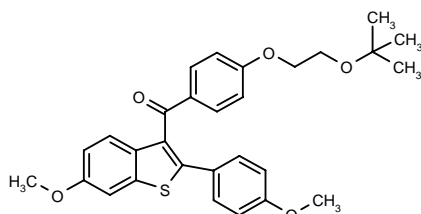
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2. Yang, L. et al. *Thiazole-derived potent, highly bioavailable short duration growth hormone secretagogue L-165,666*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 074.

TREATMENT OF GYNECOLOGICAL DISORDERS

273716

1-[4-[2-(*tert*-Butoxy)ethoxy]phenyl]-1-[6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl]methanone



C29 H30 O5 S; Mol wt: 490.6170

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancers such as breast, uterine and cervical cancer. Compound is reported to decrease serum cholesterol levels in ovariectomized rats with little stimulatory effect on the uterus or on eosinophil infiltration into the uterus, contrary to the effects observed with 17 α -ethinylestradiol. A representative compound from a series of specifically claimed benzo[*b*]thiophene derivatives.

SOURCE – Lilly.

REFERENCES

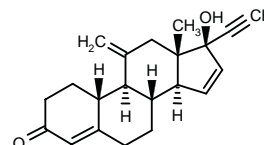
1. Bryant, H.U. and Dodge, J.A. (Eli Lilly and Company) *Benzothiophenes*. EP 902025, WO 9907693.

CONTRACEPTIVES

ORG-30659***129867**

(17 α)-17-Hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one

17 α -Ethinyl-17 β -hydroxy-11-methyleneestra-4,15-dien-3-one



C21 H24 O2; Mol wt: 308.4186

ACTION – Potent progestagen currently under clinical development as an oral contraceptive and for hormone replacement therapy. It exerts progestational activity similar to that of etonogestrel but more potent than that of levonorgestrel and norethisterone. Compound is devoid of androgenic activity, as well as glucocorticoid and antiglucocorticoid activities.

SOURCE – Organon.

REFERENCES

1. Bergink, E.W. (Akzo Nobel N.V.) *Novel 11-methylene-oestr-15-enes, processes for their preparation, and pharmaceutical compsns*. AU 8660162, EP 210678, ES 8802233, JP 87030799, US 5236913.
2. Booy, C.J. et al. (Akzo Nobel N.V.) *Novel crystalline form of the progestagen-(17 α) 17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one (Org 30659)*. EP 897927.
3. de Haan, P. and Poels-Janssen, H.G.M. (Akzo Nobel N.V.) *Solid pharmaceutical compsn. comprising an excipient capable of binding water*. EP 707848.
4. De Haan, P. and Zwinkels, J.A.M. (Akzo Nobel N.V.) *Process of making dosage units by wet granulation*. WO 9609056.
5. Bergink, W. et al. *Serum pharmacokinetics of orally administered desogestrel and binding of contraceptive progestogens to sex hormone-binding globulin*. Am J Obstet Gynecol 1990, 163(6, Part 2): 2132.
6. Kalkhoven, E. et al. *Synthetic progestins in breast tumor cells. Regulation of proliferation and receptor activation*. Ann New York Acad Sci 1993, 684: 220.
7. Liu, L.-G. et al. *Regio- and stereoselective hydrogenation of 17-substituted 13 β -ethyl-11 β -hydroxy-gona-4,9-dien-3-ones and NMR study*. Tetrahedron 1996, 52(12): 4495.
8. Schoonen, W.G.E.J. et al. *Effects of two classes of progestagens, pregnane and 19-nortestosterone derivatives, on cell growth of human breast tumor cells: I. MCF-7 cell lines*. J Steroid Biochem Mol Biol 1995, 55(3-4): 423.
9. Schoonen, W.G.E.J. et al. *Effects of two classes of progestagens, pregnane and 19-nortestosterone derivatives, on cell growth of human breast tumor cells: II. T47D cell lines*. J Steroid Biochem Mol Biol 1995, 55(3-4): 439.
10. van der Burg, B. et al. *Effects of progestins on the proliferation of estrogen-dependent human breast cancer cells under growth factor-defined conditions*. J Steroid Biochem Mol Biol 1992, 42(5): 457.
11. van der Burg, B. et al. *Regulation of proliferation of estrogen-dependent human breast cancer cells by synthetic progestins*. Adv Contracept 1992, 8(3): 195.

12. Verhoeven, C.H.J. et al. *In vitro and in vivo metabolism of the progestagen Org 30659 in several species*. Drug Metab Dispos 1998, 26(11): 1102.

13. Akzo Nobel Product Pipeline 1995, September.

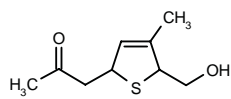
*Identified compound **129867** Drug Data Rep 1987, 009(07): 0602.

DERMATOLOGIC DRUGS

ACNE THERAPY

273953

1-[5-(Hydroxymethyl)-4-methyl-2,5-dihydro-2-thienyl]-2-propanone



C9 H14 O2 S; Mol wt: 186.2736

ACTION – New *all-trans*-retinol metabolite produced by *in vitro* incubation of *all-trans*-retinol with kidney homogenates from vitamin A-deficient and retinoic acid-supplemented female rats, reported to be potentially useful for the treatment of alopecia and skin disorders such as acne, ichthyosis, psoriasis, wrinkles and UV light skin damage, as well as for use as an anticancer agent and for promoting female fertility and maintaining pregnancy.

SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

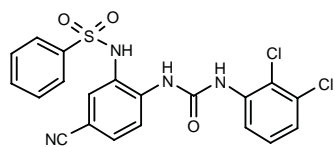
REFERENCES

1. DeLuca, H.F. et al. (Wisconsin Alumni Research Foundation) *All-trans-retinol metabolite*. US 5880292, WO 9912922.

ANTIPSORIATICS

273908

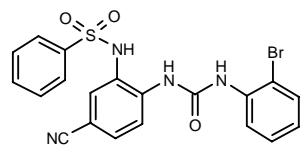
N-[5-Cyano-2-[3-(2,3-dichlorophenyl)ureido]phenyl]-benzenesulfonamide



C20 H14 Cl2 N4 O3 S; Mol wt: 461.3276

ACTION – Potent chemokine CXCR2 receptor antagonist (IC₅₀ = 60 nM) with about 900-fold selectivity over CXCR1 receptors. Potentially useful in the treatment of inflammatory diseases related to excessive production of

IL-8 such as psoriasis, bronchial asthma, arthritis, inflammatory bowel disease, septic shock, cardiac and renal reperfusion injury, Alzheimer's disease, glomerulonephritis and graft-vs.-host reactions. Another compound from this series of phenyl urea compounds is:



273907: C20 H15 Br N4 O3 S

SOURCE – SmithKline Beecham.

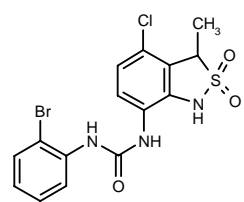
REFERENCES

1. Widdowson, K.L. et al. (SmithKline Beecham plc) *IL-8 receptor antagonists*. EP 809492, JP 99503110, US 5780483, WO 9625157.

2. Nie, H. et al. *Discovery and characterization of a novel series of N-[2-(phenylsulfonylamino)phenyl]-N'-phenylureas as CXCR2 antagonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 205.

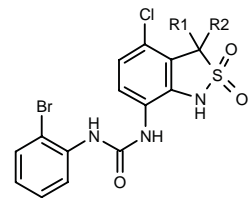
274912

N-(2-Bromophenyl)-N'-(4-chloro-3-methyl-2,2-dioxo-1,3-dihydro-2,1-benzisothiazol-7-yl)urea



C15 H13 Br Cl N3 O3 S; Mol wt: 430.7087

ACTION – Chemokine CXCR1 and/or CXCR2 (formerly IL-8) receptor antagonist with potential in the treatment of chemokine-mediated disorders such as psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, stroke, reperfusion injury, glomerulonephritis, thrombosis, atherosclerosis, bone resorption disorders, Alzheimer's disease and transplant rejection. Other specifically claimed compounds from this series of substituted 2,1-benzisothiazole derivatives include the following:



Compound	R1	R2	Formula
274913	H	Pr	C ₁₇ H ₁₇ BrClN ₃ O ₃ S
274914	Me	Me	C ₁₆ H ₁₅ BrClN ₃ O ₃ S
274915	H	F	C ₁₄ H ₁₀ BrClFN ₃ O ₃ S
274916	H	CH ₂ CONH ₂	C ₁₆ H ₁₄ BrClN ₄ O ₄ S
274917	Me	CH ₂ CONH ₂	C ₁₇ H ₁₆ BrClN ₄ O ₄ S
274918		-CH ₂ -	C ₁₅ H ₁₁ BrClN ₃ O ₃ S
274921	H	2-benzothiazolyl	C ₂₁ H ₁₄ BrClN ₄ O ₃ S ₂

12. Verhoeven, C.H.J. et al. *In vitro and in vivo metabolism of the progestagen Org 30659 in several species.* Drug Metab Dispos 1998, 26(11): 1102.

13. Akzo Nobel Product Pipeline 1995, September.

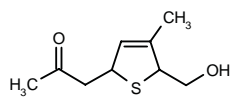
*Identified compound **129867** Drug Data Rep 1987, 009(07): 0602.

DERMATOLOGIC DRUGS

ACNE THERAPY

273953

1-[5-(Hydroxymethyl)-4-methyl-2,5-dihydro-2-thienyl]-2-propanone



C9 H14 O2 S; Mol wt: 186.2736

ACTION – New *all-trans*-retinol metabolite produced by *in vitro* incubation of *all-trans*-retinol with kidney homogenates from vitamin A-deficient and retinoic acid-supplemented female rats, reported to be potentially useful for the treatment of alopecia and skin disorders such as acne, ichthyosis, psoriasis, wrinkles and UV light skin damage, as well as for use as an anticancer agent and for promoting female fertility and maintaining pregnancy.

SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

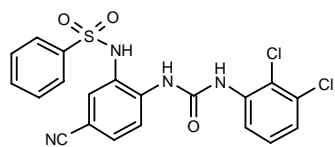
REFERENCES

1. DeLuca, H.F. et al. (Wisconsin Alumni Research Foundation) *All-trans-retinol metabolite.* US 5880292, WO 9912922.

ANTIPSORIATICS

273908

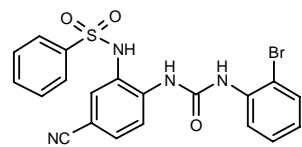
N-[5-Cyano-2-[3-(2,3-dichlorophenyl)ureido]phenyl]-benzenesulfonamide



C20 H14 Cl2 N4 O3 S; Mol wt: 461.3276

ACTION – Potent chemokine CXCR2 receptor antagonist (IC₅₀ = 60 nM) with about 900-fold selectivity over CXCR1 receptors. Potentially useful in the treatment of inflammatory diseases related to excessive production of

IL-8 such as psoriasis, bronchial asthma, arthritis, inflammatory bowel disease, septic shock, cardiac and renal reperfusion injury, Alzheimer's disease, glomerulonephritis and graft-vs.-host reactions. Another compound from this series of phenyl urea compounds is:



273907: C20 H15 Br N4 O3 S

SOURCE – SmithKline Beecham.

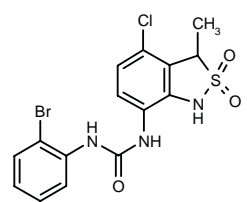
REFERENCES

1. Widdowson, K.L. et al. (SmithKline Beecham plc) *IL-8 receptor antagonists.* EP 809492, JP 99503110, US 5780483, WO 9625157.

2. Nie, H. et al. *Discovery and characterization of a novel series of N-[2-(phenylsulfonylamino)phenyl]-N'-phenylureas as CXCR2 antagonists.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 205.

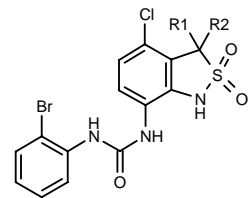
274912

N-(2-Bromophenyl)-N'-(4-chloro-3-methyl-2,2-dioxo-1,3-dihydro-2,1-benzisothiazol-7-yl)urea



C15 H13 Br Cl N3 O3 S; Mol wt: 430.7087

ACTION – Chemokine CXCR1 and/or CXCR2 (formerly IL-8) receptor antagonist with potential in the treatment of chemokine-mediated disorders such as psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, stroke, reperfusion injury, glomerulonephritis, thrombosis, atherosclerosis, bone resorption disorders, Alzheimer's disease and transplant rejection. Other specifically claimed compounds from this series of substituted 2,1-benzisothiazole derivatives include the following:



Compound	R1	R2	Formula
274913	H	Pr	C ₁₇ H ₁₇ BrClN ₃ O ₃ S
274914	Me	Me	C ₁₆ H ₁₅ BrClN ₃ O ₃ S
274915	H	F	C ₁₄ H ₁₀ BrClFN ₃ O ₃ S
274916	H	CH ₂ CONH ₂	C ₁₆ H ₁₄ BrClN ₄ O ₄ S
274917	Me	CH ₂ CONH ₂	C ₁₇ H ₁₆ BrClN ₄ O ₄ S
274918		-CH ₂ -	C ₁₅ H ₁₁ BrClN ₃ O ₃ S
274921	H	2-benzothiazolyl	C ₂₁ H ₁₄ BrClN ₄ O ₃ S ₂

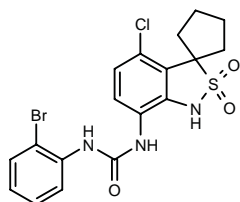
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Nie, H. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9911264.

274932

N-(2-Bromophenyl)-*N'*-[4-chloro-2,2-dioxospiro[2,1-benzisothiazol-3(1*H*),1'-cyclopentan]-7-yl]urea



C18 H17 Br Cl N3 O3 S; Mol wt: 470.7733

ACTION – Chemokine CXCR1 and/or CXCR2 (formerly IL-8) receptor antagonist with potential in the treatment of chemokine-mediated disorders such as psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, stroke, reperfusion injury, glomerulonephritis, thrombosis, atherosclerosis, bone resorption disorders, Alzheimer's disease and transplant rejection.

SOURCE – SmithKline Beecham.

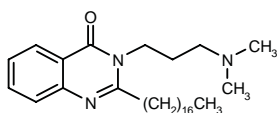
REFERENCES

1. Nie, H. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9911253.

HAIR GROWTH STIMULANTS

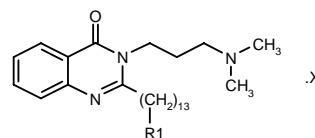
274747

3-[3-(Dimethylamino)propyl]-2-heptadecyl-4(3*H*)-quinazolinone



C30 H51 N3 O; Mol wt: 469.7529

ACTION – Topical hair growth promoter proven to stimulate 100% regrowth of hair on the backs of mice within 18 days of hair removal when applied at a concentration of 0.1% w/v daily throughout the experiment. Other compounds from this series of quinazolin-4-one derivatives include the following:



Compound	R1	X	Formula
274748	Bu	HCl	C ₃₀ H ₅₁ N ₃ O.HCl
274749	Bu	2HCl	C ₃₀ H ₅₁ N ₃ O.2HCl
274751	H		C ₂₆ H ₄₃ N ₃ O
274752	C8H17	HCl	C ₃₄ H ₅₉ N ₃ O.HCl

SOURCE – Shiseido.

REFERENCES

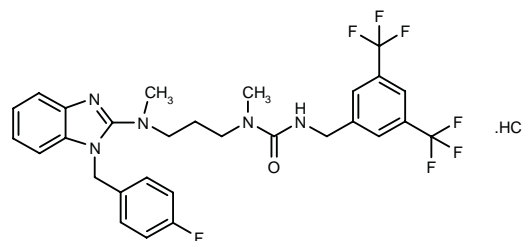
1. Kobayashi, K. et al. (Shiseido Co. Ltd.) *Quinazolin-4-one derivs., their preparation and their use as hair growth promoters or in external compns. for skin*. EP 903344, JP 99124370.

TOPICAL ANTIALLERGIC DRUGS

NIP-530*

271479

N'-[3,5-Bis(trifluoromethyl)benzyl]-*N*-[3-[*N*-[1-(4-fluorobenzyl)benzimidazol-2-yl]-*N*-methylamino]propyl]-*N*-methylurea hydrochloride



C29 H28 F7 N5 O . HCl; Mol wt: 632.0211

ACTION – Dual NK₁ and histamine H₁ receptor antagonist (K_i = 1 and 0.56 μM, respectively, using human NK₁ and bovine H₁ receptors) found to inhibit the production of IL-4 and IL-5 in concanavalin A-stimulated human peripheral blood mononuclear cells and of 5-lipoxygenase in human granulocytes. *In vivo*, compound (3-30 mg/kg p.o.) prevented substance P-, histamine- or ovalbumin-induced scratching behavior in mice and inhibited the allergic response to DNFB in mouse ears. Potentially useful for the treatment of atopic dermatitis.

SOURCE – Nissan Chemical.

REFERENCES

1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Benzimidazole deriv.* WO 9850368.
2. Hirozuka, M. et al. *Search of novel therapeutic agent for atopic dermatitis: Approach with dual tachykinin NK/histamine H1 receptor antagonist*. 119th Annu Meet Pharm Soc Jpn (March 29-31, Tokushima) 1999, Abst 29(PO)10-091.
3. Yamamoto, A. et al. *Pharmacological properties of NIP-530, a novel therapeutic agent for atopic dermatitis*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-663.

*Identified compound **271479** Drug Data Report 1999, 021(02): 0127.

WOUND-HEALING AGENTS

HBGF-0.8

273717

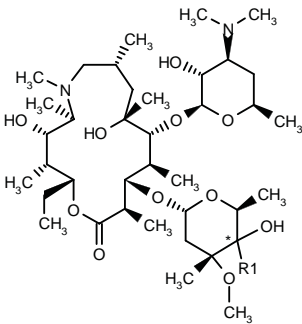
Heparin-binding growth factor polypeptide

ACTION – Heparin-binding growth factor (HBGF) polypeptide corresponding to the carboxy-terminal portion of connective tissue growth factor (CTGF) that exhibits many of the functional characteristics of full-length CTGF and thus possesses mitogenic and chemotactic properties. Claimed for the treatment of atherosclerosis or fibrotic, sclerotic or proliferative disorders, as well as for accelerating wound healing.

SOURCE – Children’s Hospital Research Foundation, Columbus, OH (US).

REFERENCES

1. Brigstock, D.A. and Harding, P.A. (Children’s Hospital Research Foundation) Heparin-binding growth factor (HBGF) polypeptides. WO 9907407.



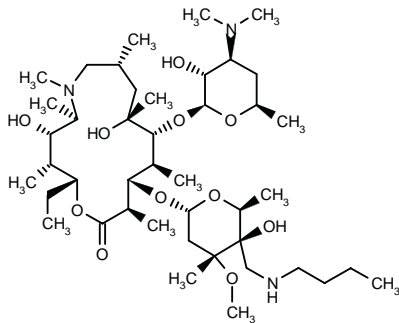
Compound	R1	*Isomer	Formula
274185	CH2N(CH2CH2OH)2	R	C ₄₃ H ₈₃ N ₃ O ₁₃
274186	1-imidazolyl-CH2	R	C ₄₂ H ₇₆ N ₄ O ₁₁
274187	1,2,4-triazol-1-yl	R	C ₄₁ H ₇₅ N ₅ O ₁₁
274188	MeOCH2-ethynylene	RS	C ₄₂ H ₇₆ N ₂ O ₁₂
274189	CN	RS	C ₃₉ H ₇₁ N ₃ O ₁₁
274190	1-Pip-CH2	S	C ₄₄ H ₈₃ N ₃ O ₁₁
274193	4-CF3-PhCH2NH-CH2CH2NHCCH2	R	C ₄₉ H ₈₅ F ₃ N ₄ O ₁₁

ANTIINFECTIVE THERAPY

ANTIBIOTICS

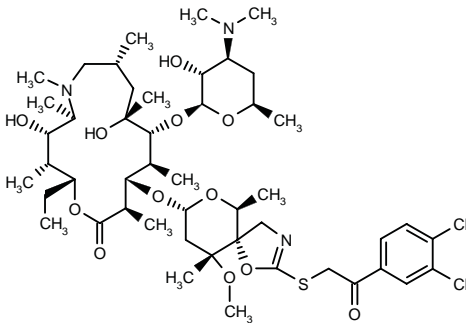
274184

4''-(Butylaminomethyl)-9-deoxo-4''(R)-hydroxy-9a-methyl-9a-aza-9a-homoerythromycin A

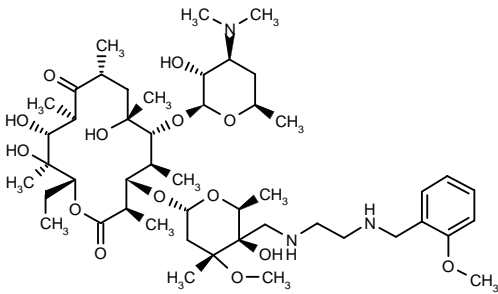


C43 H83 N3 O11; Mol wt: 818.1387

ACTION – Antibacterial and antiprotozoal agent from a series of C-4''-substituted macrolide derivatives, wherein the following are also included:



274192: C48 H77 Cl2 N3 O12 S



274194: C48H83N3O14

SOURCE – Pfizer.

REFERENCES

1. Bronk, B.S. et al. (Pfizer Products Inc.) C-4''-Substd. macrolide derivs. WO 9856801.

WOUND-HEALING AGENTS

HBGF-0.8

273717

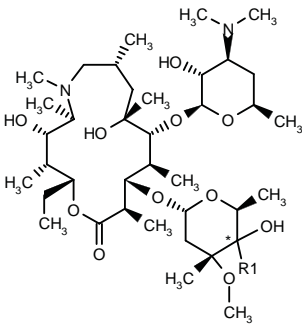
Heparin-binding growth factor polypeptide

ACTION – Heparin-binding growth factor (HBGF) polypeptide corresponding to the carboxy-terminal portion of connective tissue growth factor (CTGF) that exhibits many of the functional characteristics of full-length CTGF and thus possesses mitogenic and chemotactic properties. Claimed for the treatment of atherosclerosis or fibrotic, sclerotic or proliferative disorders, as well as for accelerating wound healing.

SOURCE – Children’s Hospital Research Foundation, Columbus, OH (US).

REFERENCES

1. Brigstock, D.A. and Harding, P.A. (Children’s Hospital Research Foundation) Heparin-binding growth factor (HBGF) polypeptides. WO 9907407.



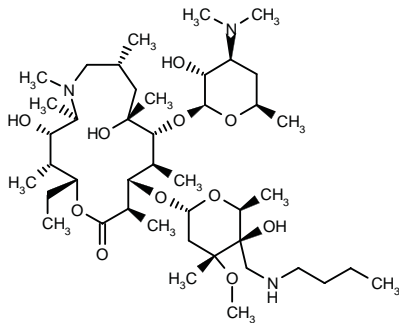
Compound	R1	*Isomer	Formula
274185	CH2N(CH2CH2OH)2	R	C ₄₃ H ₈₃ N ₃ O ₁₃
274186	1-imidazolyl-CH2	R	C ₄₂ H ₇₆ N ₄ O ₁₁
274187	1,2,4-triazol-1-yl	R	C ₄₁ H ₇₅ N ₅ O ₁₁
274188	MeOCH2-ethynylene	RS	C ₄₂ H ₇₆ N ₂ O ₁₂
274189	CN	RS	C ₃₉ H ₇₁ N ₃ O ₁₁
274190	1-Pip-CH2	S	C ₄₄ H ₈₃ N ₃ O ₁₁
274193	4-CF3-PhCH2NH-CH2CH2NHCH2	R	C ₄₉ H ₈₅ F ₃ N ₄ O ₁₁

ANTIINFECTIVE THERAPY

ANTIBIOTICS

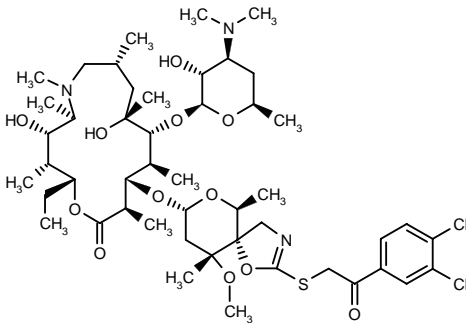
274184

4''-(Butylaminomethyl)-9-deoxo-4''(R)-hydroxy-9a-methyl-9a-aza-9a-homoerythromycin A

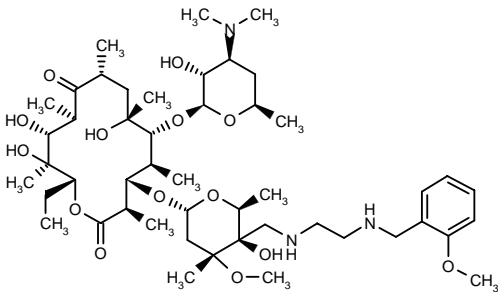


C43 H83 N3 O11; Mol wt: 818.1387

ACTION – Antibacterial and antiprotozoal agent from a series of C-4''-substituted macrolide derivatives, wherein the following are also included:



274192: C48 H77 Cl2 N3 O12 S



274194: C48H83N3O14

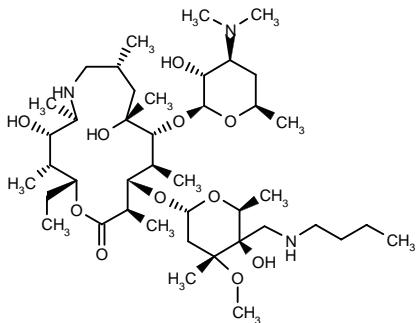
SOURCE – Pfizer.

REFERENCES

1. Bronk, B.S. et al. (Pfizer Products Inc.) C-4''-Substd. macrolide derivs. WO 9856801.

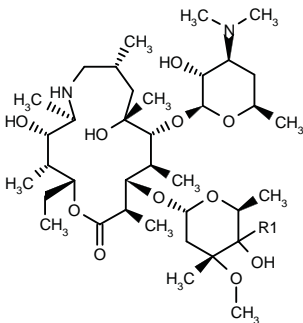
274195

4''-(Butylaminomethyl)-9-deoxo-4''(*R*)-hydroxy-9a-aza-9a-homoerythromycin A



C42 H81 N3 O11; Mol wt: 804.1119

ACTION – Antibacterial and antiprotozoal agent from a series of 4''-substituted-9-deoxo-9a-aza-9a-homoerythro-mycin A derivatives, wherein the following are also included:



Compound	R1	Formula
274196	cyclopentyl-NHCH2	C ₄₃ H ₈₁ N ₃ O ₁₁
274197	CH2NHCH2CH(Me)OMe	C ₄₂ H ₈₁ N ₃ O ₁₂
274198	1,2,3-triazolyl-1-yl-CH2	C ₄₀ H ₇₃ N ₅ O ₁₁
274199	allyl	C ₄₀ H ₇₄ N ₃ O ₁₁
274200	2-Pyr-ethynylene	C ₄₄ H ₇₃ N ₃ O ₁₁
274201	ethynylene-(CH2)3CN	C ₄₃ H ₇₅ N ₃ O ₁₁
274202	CH2NHPr	C ₄₁ H ₇₉ N ₃ O ₁₁
274203	1-azetidinyl-CH2	C ₄₁ H ₇₇ N ₃ O ₁₁
274204	1-Pip-CH2	C ₄₃ H ₈₁ N ₃ O ₁₁
274205	3,4-(F)2-PhCH2NHCH2	C ₄₅ H ₇₇ F ₂ N ₃ O ₁₁

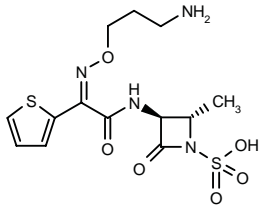
SOURCE – Pfizer.

REFERENCES

1. Bronk, B.S. et al. (Pfizer Products Inc.) 4''-Substd.-9-deoxo-9a-aza-9a-homoerythromycin A derivs. WO 9856802.

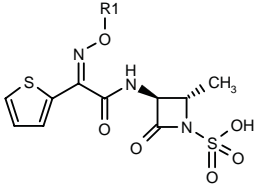
274477

(2*S*,3*S*)-3-[2(*E*)-(3-Aminopropoxyimino)-2-(2-thienyl)-acetamido]-2-methyl-4-oxoazetidine-1-sulfonic acid



C13 H18 N4 O6 S2; Mol wt: 390.4392

ACTION – Potent β -lactamase inhibitor, particularly active against class C β -lactamases (cephalosporinases), for use in combination with β -lactam antibiotics to increase their effectiveness against infections caused by β -lactamase-producing bacteria, particularly *Pseudomonas aeruginosa*. Compound exhibited an IC₅₀ value of 0.02 μ M against cephalosporinase from *P. aeruginosa* compared to a value of 0.13 μ M for the reference compound aztreonam. It exhibited excellent synergy when given in combination with ceftazidime at a concentration of 10 μ g/ml; for example, the MIC values for ceftazidime against *Enterobacter cloacae* 40054, *Morganella morganii* 36014 and *P. aeruginosa* 46220 DR-2-1 were < 0.25, < 0.25 and 2.0 μ g/ml, respectively, when given with title comopund compared to values of > 32, > 32 and > 32 μ g/ml, respectively, when ceftadizime was given alone or in combination with aztreonam. A representative compound from a series of azetidinone derivatives, wherein the following are also included:



Compound	R1	Formula
274486	CH(CH2NH2)2	C ₁₃ H ₁₉ N ₅ O ₆ S ₂
274487	CH(CH2OH)CH2NH2	C ₁₃ H ₁₈ N ₄ O ₇ S ₂
274488	CH2CH(NH2)CH2OH	C ₁₃ H ₁₈ N ₄ O ₇ S ₂
274489	CH(Me)CH2NH2	C ₁₃ H ₁₉ N ₄ O ₆ S ₂

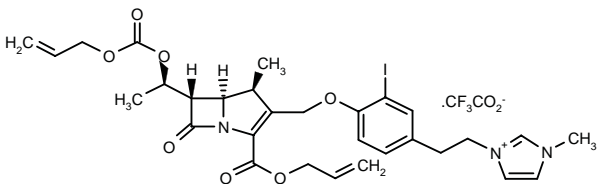
SOURCES – Synphar; Taiho.

REFERENCES

1. Maiti, S.N. et al. (Synphar Laboratories Inc.;Taiho Pharmaceutical Co., Ltd.) Azetidinone derivs. as beta-lactamase inhibitors. WO 9910324.

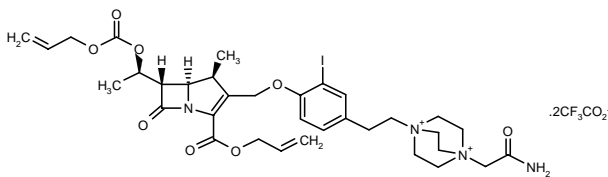
275276

(1*S*,5*R*,6*S*)-3-[2-[4-[3-(Allyloxycarbonyl)-6-[1(*R*)-(allyloxycarbonyloxy)ethyl]-1-methyl-1-carba-2-penem-2-yl]methoxy]-3-iodophenyl]ethyl]-1-methylimidazolium trifluoroacetate

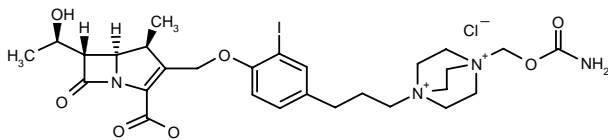


C30 H35 I N3 O7 . C2 F3 O2; Mol wt: 789.5345

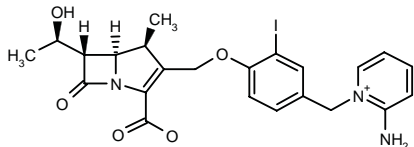
ACTION – Carbapenem antibiotic reported to be effective against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other specifically claimed compounds from this series of 3-(iodophenoxymethyl)carbapenem derivatives include the following:



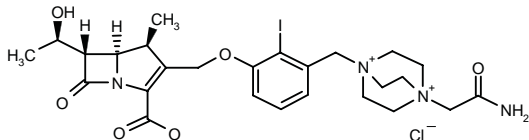
275277: C38 H45 F6 I N4 O12



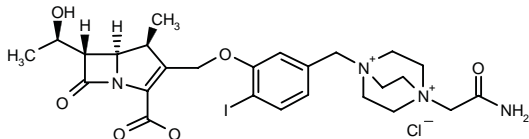
275278: C28 H38 Cl I N4 O7



275279: C23 H24 I N3 O5



275280: C26 H34 Cl I N4 O6



275281: C26 H34 Cl I N4 O6

SOURCE – Merck & Co.

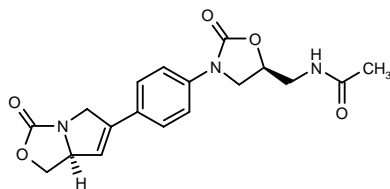
REFERENCES

1. Dininno, F.P. and Dykstra, K.D. (Merck & Co., Inc.) *3-(Iodophenoxymethyl) carbapenem antibacterials*. WO 9912928.

ANTIBACTERIAL DRUGS

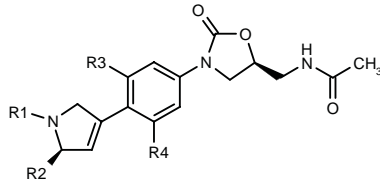
274783

N-[3-[4-[3-Oxo-5,7a(*S*)-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-6-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide

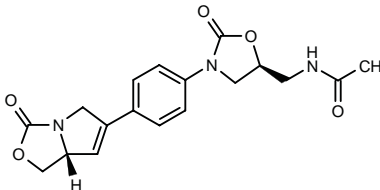


C18 H19 N3 O5; Mol wt: 357.3641

ACTION – Oxazolidinone antibacterial agent active against Gram-positive organisms such as *Staphylococcus aureus* Oxford (MIC = 0.25 µg/ml), methicillin/quinolone-resistant *S. aureus* (MIC = 2.0 µg/ml), methicillin-sensitive coagulase-negative staphylococci (MIC = 0.13 µg/ml), methicillin-resistant coagulase-negative staphylococci (MIC = 0.50 µg/ml), *Streptococcus pyogenes* C203 (MIC = 0.13 µg/ml), *Enterococcus faecalis* (MIC = 0.50 µg/ml) and *Bacillus subtilis* (MIC = 0.50 µg/ml). Other specifically claimed compounds from this series of oxazolidinone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
274784	SO2Me	CO2CH2Ph	H	H	C ₂₅ H ₂₇ N ₃ O ₇ S
274786	CN	CO2CH2Ph	H	H	C ₂₅ H ₂₄ N ₄ O ₅
274787	CHO	CO2CH2Ph	H	H	C ₂₅ H ₂₅ N ₃ O ₆
274788	CN	2-pyrimidinyl-SCH2	H	H	C ₂₂ H ₂₂ N ₆ O ₃ S
274790	CN	CH2OCOPh	H	H	C ₂₅ H ₂₄ N ₄ O ₅
274791	CHO	CH2OCOPh	H	H	C ₂₅ H ₂₅ N ₃ O ₆
274792	-CH2OCO-		F	H	C ₁₈ H ₁₈ FN ₃ O ₅
274793	-CH2OCO-		F	F	C ₁₈ H ₁₇ F ₂ N ₃ O ₅
274795	-CH2NHCO-		H	H	C ₁₈ H ₂₀ N ₄ O ₄



274794: C18 H19 N3 O5

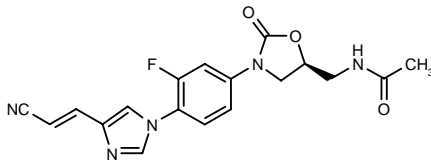
SOURCE – Zeneca (AstraZeneca).

REFERENCES

1. Gravestock, M.B. (Zeneca Ltd.) *Antibiotic oxazolidinone derivs*. WO 9910342.

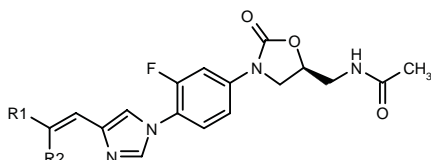
274796

N-[3-[4-[4-(2-Cyanovinyl)-1*H*-imidazol-1-yl]-3-fluorophenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C18 H16 F N5 O3; Mol wt: 369.3544

ACTION – Oxazolidinone antibacterial agent active against Gram-positive organisms such as *Staphylococcus aureus* Oxford (MIC = 0.125 µg/ml), methicillin/quinolone-resistant *S. aureus* (MIC = 1.0 µg/ml), methicillin-sensitive coagulase-negative staphylococci (MIC = 0.06 µg/ml), methicillin-resistant coagulase-negative staphylococci (MIC = 0.25 µg/ml), *Streptococcus pyogenes* C203 (MIC = 0.125 µg/ml), *Enterococcus faecalis* (MIC = 0.25 µg/ml) and *Bacillus subtilis* (MIC = 0.25 µg/ml). Other specifically claimed compounds from this series of oxazolidinone derivatives include the following:



Compound	R1	R2	Formula
274797	Br	Br	C ₁₇ H ₁₅ Br ₂ FN ₄ O ₃
274798	Br	H	C ₁₇ H ₁₆ BrFN ₄ O ₃
274799	Cl	Cl	C ₁₇ H ₁₅ Cl ₂ FN ₄ O ₃
274800	Cl	H	C ₁₇ H ₁₆ ClFN ₄ O ₃
274801	4-Pyr	H	C ₂₂ H ₂₀ FN ₅ O ₃
274802	1-oxido-2-Pyr	H	C ₂₂ H ₂₀ FN ₅ O ₄
274803	2,4-(F)2-Ph	H	C ₂₃ H ₁₉ F ₃ N ₄ O ₃
274804	2-Pyr	H	C ₂₂ H ₂₀ FN ₅ O ₃
274805	4-MeO-Ph	H	C ₂₄ H ₂₃ FN ₄ O ₄

SOURCE – Zeneca (AstraZeneca).

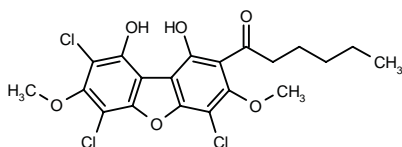
REFERENCES

1. Betts, M.J. and Roberts, D.A. (Zeneca Ltd.) *Oxazolidinone derivs. and their use as antibacterial agents*. WO 9910343.

AB-0022A

274031

2,4,6-Trichloro-8-hexanoyl-3,7-dimethoxydibenzo-[b,d]furan-1,9-diol



C20 H19 Cl3 O6; Mol wt: 461.7231

ACTION – Antibacterial agent, a dibenzofuran derivative isolated from *Dictyostelium purpureum* (K1001 strain) and *Escherichia coli* (NIHJ JC-2).

SOURCE – Kyorin.

REFERENCES

1. Aono, M. et al. (Kyorin Pharmaceutical Co., Ltd.) *Novel dibenzofuran derivs*. JP 99080146.

2. Asakawa, S. et al. *Isolation and structure of AB0022A, a cellular mucous bacteria-derived novel antibacterial compound*. 73rd Annu Congr Jpn Soc Biosci Biotechnol Agrochem (March 31-April 1, Fukuoka) 1999, Abst 3p197C.

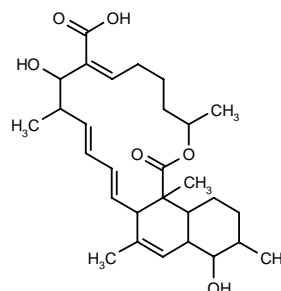
3. Sawada, T. and Aono, M. *Whole synthesis of AB0022A, a cellular mucous bacteria-derived antibacterial compound*. 73rd Annu Congr Jpn Soc Biosci Biotechnol Agrochem (March 31-April 1, Fukuoka) 1999, Abst 3p198D.

ANTIMYCOBACTERIAL AGENTS

TUBELACTOMICIN A

274030

9,17-Dihydroxy-3,10,15,18,20b-pentamethyl-1-oxo-3,4,5,6,9,10,14a,16a,17,18,19,20,20a,20b-tetradecahydro-1H-naphth[1,2-c]oxacyclohexadecine-8-carboxylic acid



C29 H42 O6; Mol wt: 486.6448

ACTION – Antibiotic isolated from *Nocardia* sp. MK703102F1 with specific activity against acid-fast bacteria such as *Mycobacterium vaccae* (MIC = 0.1 µg/ml). No toxicity was observed in mice at the dose of 100 mg/kg i.v.

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

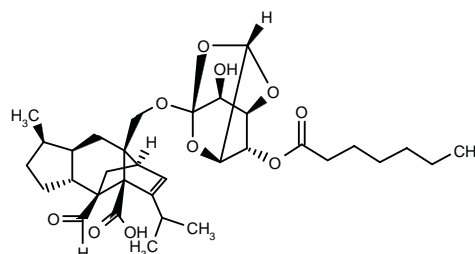
REFERENCES

1. Igarashi, M. et al. *Study of tubelactomicin A, a novel antibiotic*. 73rd Annu Congr Jpn Soc Biosci Biotechnol Agrochem (March 31-April 1, Fukuoka) 1999, Abst 3p210D.

ANTIFUNGAL AGENTS

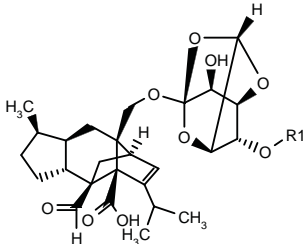
273063

[1R,3aR,4S,4aR,7R,7aR,8aS(2S,3aR,5S,6S,6aR,7S)]-4-Formyl-8a-[6-(heptanoyloxy)-7-hydroxyperhydro-2,5-methanofuro[2,3-d][1,3]dioxol-2-ylloxymethyl]-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-s-indacene-3a-carboxylic acid



C33 H46 O10; Mol wt: 602.7164

ACTION – Antifungal agent, a derivative of the known antifungal substance BE-31405⁺ (obtained from *Penicillium* F-31405, FERM BP-5714); it had an MIC of 1.56 µg/ml against *Candida albicans* IFO 1385 compared to 50 µg/ml for BE-31405. Within this series of BE-31405 derivatives, the following are also included:



Compound	R1	Formula
273064	COBu	C ₃₁ H ₄₂ O ₁₀
273065	COC5H11	C ₃₂ H ₄₄ O ₁₀
273066	Bu	C ₃₀ H ₄₂ O ₉
273067	C5H11	C ₃₁ H ₄₄ O ₉
273068	i-BuCH2	C ₃₁ H ₄₄ O ₉
273069	C6H13	C ₃₂ H ₄₆ O ₉
273070	C10H21	C ₃₆ H ₅₄ O ₉

SOURCE – Banyu.

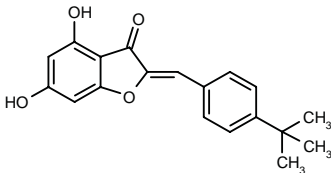
REFERENCES

1. Hirano, A. et al. (Banyu Pharmaceutical Co., Ltd.) *Derivs. of antifungal substance BE-31405 and process for producing the same*. WO 9852957.

⁺Drug Data Rep 1995, 017(08): 0745.

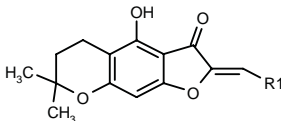
273372

2-[(*Z*)-4-*tert*-Butylbenzylidene]-4,6-dihydroxy-1-benzofuran-3(2*H*)-one



C19 H18 O4; Mol wt: 310.3472

ACTION – Antifungal agent with MIC values of 12.5, 0.39, 6.25, 6.25 and 6.25 µg/ml against *Candida albicans* ATCC 90028, fluconazole-resistant *Candida glabrata*, *Candida parapsilosis* ATCC 90018, *Candida krusei* ATCC 6258 and *Aspergillus fumigatus* 94-2766, respectively. Other compounds from this series of aurone derivatives obtained by combinatorial chemistry include the following:



Compound	R1	Formula
273373	3,4-(MeO)2-Ph	C ₂₂ H ₂₂ O ₆
273374	bicyclo[2.2.1]hept-5-en-2-yl	C ₂₁ H ₂₂ O ₄

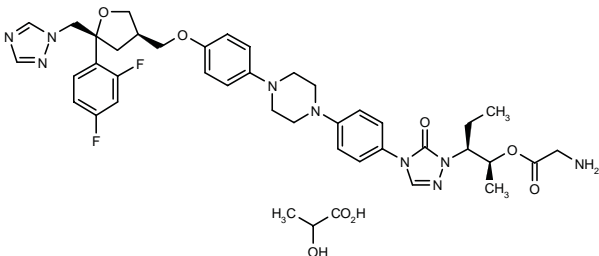
SOURCE – Phytera.

REFERENCES

1. Chu, W.-L.A. et al. (Phytera, Inc.) *Substd. aurone derivs*. WO 9904789.

274093

Glycine 2(*S*)-[4-[4-[4-[5(*R*)-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)tetrahydrofuran-3(*R*)-yl-methoxy]phenyl]piperazin-1-yl]phenyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-1(*S*)-methylbutyl ester lactate



C39 H45 F2 N9 O5 . C3 H6 O3; Mol wt: 847.9159

ACTION – Novel lactate salt of a known triazole antifungal agent*, reported to possess greatly improved solubility relative to the free base and previously described salts, thus being particularly suitable for the preparation of intravenous formulations.

SOURCE – Schering-Plough.

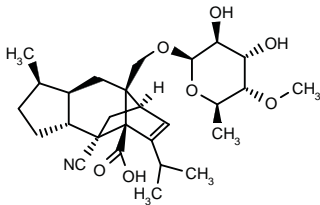
REFERENCES

1. Lovey, R.G. et al. (Schering Corp.) *Soluble azole antifungal salt*. US 5883097.

*See 245880 Drug Data Report 1997, 019(04): 0351.

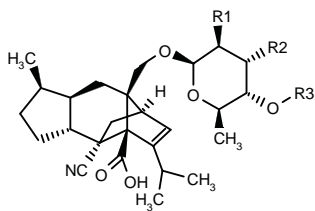
274368

[1*R*-(1α,3αβ,4β,4αβ,7β,7αα,8αβ)]-4-Cyano-8a-(6-deoxy-4-*O*-methyl-β-*D*-altropyranosyloxymethyl)-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-*s*-indacene-3a-carboxylic acid

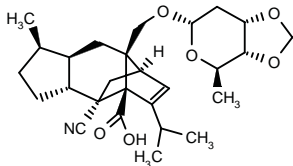


C27 H39 N O7; Mol wt: 489.6051

ACTION – Antifungal agent with a broad spectrum of activity. Other specifically claimed compounds from this series of 4-cyano-4-deformylsordarin derivatives include the following:



Compound	R1	R2	R3	Formula
274369	OH	OH	H	C ₂₆ H ₃₇ NO ₇
274370	H	-OCH2-		C ₂₇ H ₃₇ NO ₆
274371	H	-(R)-CH(Me)CH2-		C ₂₉ H ₄₁ NO ₅
274373	H	-(S)-CH(Me)CH2-		C ₂₉ H ₄₁ NO ₅
274374	H	-C(=CH)CH2-		C ₂₉ H ₃₉ NO ₅



274372: C27 H37 N O6

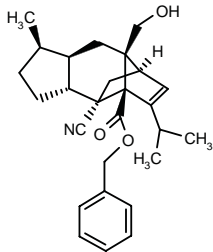
SOURCE – Merck & Co.

REFERENCES

1. Nielsen-Kahn, J. and Tse, B. (Merck & Co., Inc.) 4-Cyano-4-deformylsordarin derivs. WO 9909974.

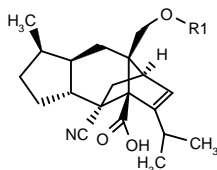
274375

[1*R*-(1α,3αβ,4β,4αβ,7β,7αα,8αβ)]-4-Cyano-8a-(hydroxymethyl)-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-*s*-indacene-3a-carboxylic acid benzyl ester



C27 H33 N O3; Mol wt: 419.5617

ACTION – Antifungal agent with a broad spectrum of activity, reported to be active against yeasts, filamentous fungi and protozoa. Other compounds from this series of 4-cyano-4-deformylsordarin derivatives include the following:



Compound	R1	Formula
274376	Ac	C ₂₂ H ₂₉ NO ₄
274377	Me	C ₂₁ H ₂₉ NO ₃
274378	(S)-CH2CH(OH)Me	C ₂₃ H ₃₃ NO ₄
274379	(R)-CH2CH(OH)Me	C ₂₃ H ₃₃ NO ₄

SOURCE – Merck & Co.

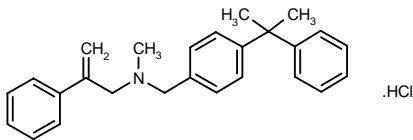
REFERENCES

1. Tse, B. (Merck & Co., Inc.) 4-Cyano-4-deformylsordarin derivs. WO 9909975.

AD-079

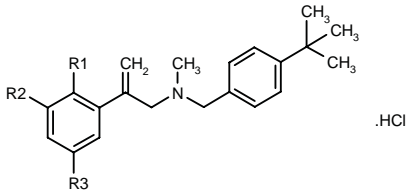
273657

N-Methyl-*N*-[4-(1-methyl-1-phenylethyl)benzyl]-*N*-(2-phenyl-2-propenyl)amine hydrochloride

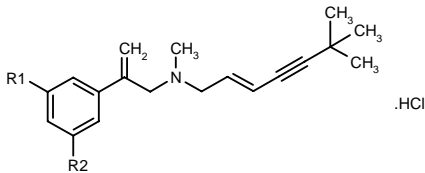


C26 H29 N . HCl; Mol wt: 391.9830

ACTION – Antifungal agent with MIC values of 0.1, 0.05, 0.2, 0.1 and 0.1 µg/ml, respectively, when tested *in vitro* against *Trichophyton mentagrophytes* IFO5811, *Trichophyton rubrum* IFO5808, *Trichophyton violaceum* TIMM1264, *Microsporum gypseum* IFO8231 and *Microsporum canis* TIMM0760. Other exemplified compounds from this series of amine derivatives are:



Compound	R1	R2	R3	Formula
AD-016 [273658]	F	H	H	C ₂₁ H ₂₆ FN.HCl
AD-022 [273659]	H	Br	H	C ₂₁ H ₂₆ BrN.HCl
AD-025 [273660]	H	Me	H	C ₂₂ H ₂₉ N.HCl
AD-074 [273661]	H	F	F	C ₂₁ H ₂₅ F ₂ N.HCl



Compound	R1	R2	Formula
PR-1484 [273662]	Br	H	C ₁₉ H ₂₄ BrN.HCl
PR-1540 [273663]	Me	H	C ₂₀ H ₂₇ N.HCl
PR-1554 [273664]	CN	H	C ₂₀ H ₂₄ N ₂ .HCl
PR-2159 [273666]	F	F	C ₁₉ H ₂₃ F ₂ N.HCl

SOURCE – Pola Chemical.

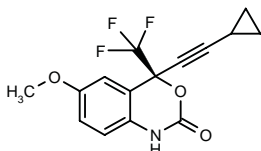
REFERENCES

1. Itoh, T. et al. (Pola Chemical Industries Inc.) Amine derivs. and process for producing the same. WO 9907666.

AIDS MEDICINES

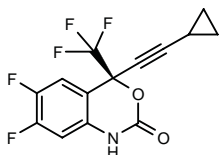
274078

4(*S*)-(Cyclopropylethynyl)-6-methoxy-4-(trifluoromethyl)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one



C₁₅ H₁₂ F₃ N O₃; Mol wt: 311.2578

ACTION – Anti-HIV agent, an HIV-1 reverse transcriptase inhibitor (IC₅₀ = 131 nM) with potent antiviral activity *in vitro* (IC₉₀ = 2.0 nM in HIV-1-infected cells). Another related compound from this series of efavirenz derivatives is:



274079: C₁₄ H₈ F₅ N O₂

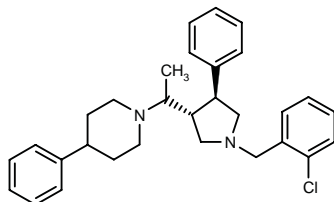
SOURCE – DuPont Pharmaceuticals.

REFERENCES

- Christ, D.D. et al. (DuPont Pharmaceuticals Co.) 4,4-Disubst.-1,4-dihydro-2*H*-3,1-benzoxazin-2-ones useful as HIV reverse transcriptase inhibitors and intermediates and processes for making the same. US 5874430.
- Christ, D.D. et al. (The Du Pont Merck Pharmaceutical Co.) 4,4-Disubst.-1,4-dihydro-2*H*-3,1-benzoxazin-2-ones useful as HIV reverse transcriptase inhibitors and intermediates and processes for making the same. WO 9814436.
- Patel, M. et al. Synthesis and evaluation of analogs of efavirenz (Sustiva(TM)) as HIV-1 reverse transcriptase inhibitors. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 173.

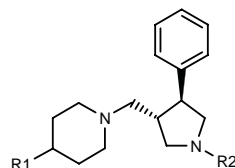
274233

(±)-*trans*-1-[1-[1-(2-Chlorobenzyl)-4-phenyl-3-pyrrolidinyl]-ethyl]-4-phenylpiperidine



C₃₀ H₃₅ Cl N₂; Mol wt: 459.0735

ACTION – Agent for the treatment of AIDS and certain immunoinflammatory disorders such as asthma, allergic diseases and rheumatoid arthritis, a modulator of chemokine receptors, including CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CXCR3 and CXCR4 receptors. Within this series of specifically claimed pyrrolidine and piperidine derivatives, the following are also included:



Compound	R1	R2	Formula
274234	Ph	2,6-(Cl)2-PhCO	C ₂₉ H ₃₀ Cl ₂ N ₂ O
274236	Ph	2-(CO ₂ Me)-PhCO	C ₃₁ H ₃₄ N ₂ O ₃
274237	Ph	1-Naph-CO	C ₃₃ H ₃₄ N ₂ O
274238	(CH ₂) ₃ Ph	cyclopentyl-CH ₂	C ₃₁ H ₄₄ N ₂
274240	(CH ₂) ₃ Ph	cyclohexyl-CH ₂	C ₃₂ H ₄₆ N ₂
274242	Ph	cyclopentyl-CO	C ₂₈ H ₃₆ N ₂ O
274243	N(Et)CO ₂ CH ₂ Ph	2-Cl-PhCO	C ₃₃ H ₃₈ ClN ₃ O ₃
274245	N(Et)CO ₂ CH ₂ Ph	COPh	C ₃₃ H ₃₉ N ₃ O ₃
274246	N(Et)CO ₂ CH ₂ Ph	cyclohexyl-CO	C ₃₃ H ₄₅ N ₃ O ₃
274247	N(Et)CO ₂ CH ₂ Ph	cyclopentyl-CO	C ₃₂ H ₄₃ N ₃ O ₃
274248	cyclohexyl-CH ₂ N(CO ₂ Me)	cyclopentyl-CO	C ₃₁ H ₄₇ N ₃ O ₃
274250	Ph	cis-2-(t-BuNHCO)-cyclohexyl-CO	C ₃₄ H ₄₇ N ₃ O ₂
274251	Ph	2-(CO ₂ Me)-cyclohexyl-CO	C ₃₁ H ₄₀ N ₂ O ₃

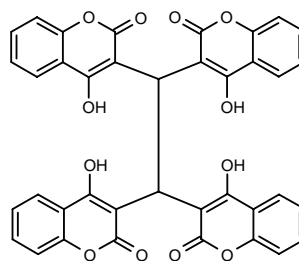
SOURCE – Merck & Co.

REFERENCES

- Budhu, R.J. et al. (Merck & Co., Inc.) Pyrrolidine and piperidine modulators of chemokine receptor activity. WO 9909984.

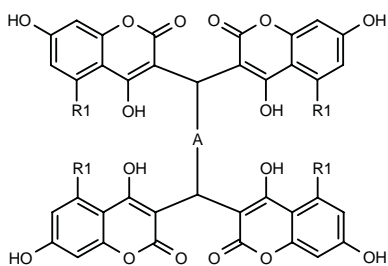
275008

3,3',3'',3'''-(Ethane-1,1,2,2-tetrayl)tetrakis(4-hydroxy-2*H*-1-benzopyran-2-one)

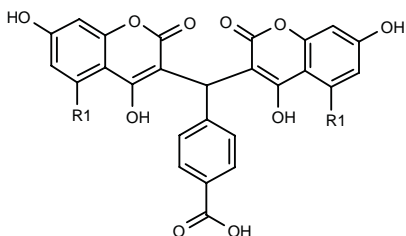


C₃₈ H₂₂ O₁₂; Mol wt: 670.5798

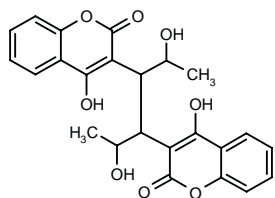
ACTION – Antiviral agent for AIDS, a representative compound from a series of hydroxy and polyhydroxy derivatives of coumarin, wherein the following are also included:



Compound	R1	A	Formula
275010	H	bond	C ₃₈ H ₂₂ O ₁₆
275011	OH	bond	C ₃₈ H ₂₂ O ₂₀
275012	OH	1,4-Ph	C ₄₄ H ₂₆ O ₂₀
275013	OH	1,3-Ph	C ₄₄ H ₂₆ O ₂₀



Compound	R1	Formula
275014	H	C ₂₆ H ₁₆ O ₁₀
275015	OH	C ₂₆ H ₁₆ O ₁₂



275009: C₂₄ H₂₂ O₈

SOURCE – Pliva.

REFERENCES

1. Trkovnik, M. and Ivezic, Z. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *Novel hydroxy and polyhydroxy derivs. of coumarin, preparation thereof and antiviral action thereof.* EP 906909.

AMANT

275016

Adamantane-containing polycarboxylic compound consisting of three components: the adamantane derivative, a nontoxic anionogenic water-soluble polycarboxylic matrix, and two dimethylenic bridges as intermediate spacer groups. It has a molecular weight of about 5kD, contains 60 carboxylic acid groups and 12% weight as adamantane

ACTION – Antiviral agent, an adamantane-containing polycarboxylic compound with activity against influenza, as well as other viruses including Eastern equine encephalomyelitis, tick-borne encephalitis and rabies virus. It was also found to selectively inhibit HIV-1 replication in MT-4 cells (IC₅₀ = 2-6 and 93 µg/ml against HIV-1 and HIV-2, respectively) with low cytotoxicity (CC₅₀ = 1200 µg/ml); compound also inhibited HIV-1 replication

in macrophages with an IC₅₀ of 20 µg/ml. It appears to act as a membranotropic drug blocking an early step of viral replication. In comparison with other adamantane derivatives such as amantadine and rimantadine, which are not effective against HIV-1 infection, compound is reported to possess much lower toxicity at the molecular, cellular and tissue levels.

SOURCE – Russian Academy of Medical Sciences, Moscow (RU).

REFERENCES

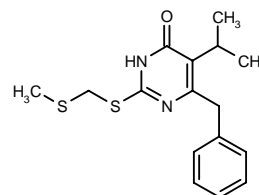
1. Burstein, M.E. et al. *Inhibition of HIV-1 replication by newly developed adamantane-containing polyanionic agents.* Antivir Res 1999, 41(3): 135.
2. Serbin, A.V. et al. *Adamantane containing antivirals: Comparative study of the known drugs and newly developed polyanionic derivatives.* Antivir Res 1999, 41(2): Abst 126.

HI-280*

265590

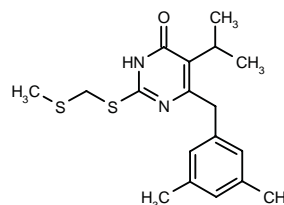
6-Benzyl-5-isopropyl-2-(methylsulfonylmethylsulfonyl)-pyrimidin-4(3H)-one

S-DABO



C₁₆ H₂₀ N₂ O S₂; Mol wt: 320.4790

ACTION – Anti-HIV agent, a non-nucleoside HIV-1 reverse transcriptase inhibitor (IC₅₀ = 6.1 µM). Compound inhibited HIV-1 replication in infected human peripheral blood mononuclear cells with an IC₅₀ < 1 nM, being slightly more potent than zidovudine and MKC-442 (emivirine). No cytotoxicity was observed at concentrations > 100 µM. Compound displayed spermicidal activity against human sperm (EC₅₀ < 200 µM), and is thus potentially useful as an active ingredient in microbial spermicides. Another compound from this series of dihydroalkoxybenzylloxypyrimidine (DABO) derivatives is:



HI-281 [274159]: C₁₈ H₂₄ N₂ O S₂

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

REFERENCES

1. D'Cruz, O.J. and Uckun, F.M. *Novel derivatives of phenethyl-5-bromopyridylthiourea (PBT) and dihydroalkoxybenzylloxypyrimidine (DABO) are spermicides with potent anti-HIV activity.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 014.
2. Mao, C. et al. *Design and analysis of non-nucleoside inhibitors for HIV-1 reverse transcriptase mutants.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 178.

3. Sudbeck, E.A. et al. *Structure-based design of novel dihydroalkoxybenzyloxy-pyrimidine derivatives as potent nonnucleoside inhibitors of the human immunodeficiency virus reverse transcriptase*. *Antimicrob Agents Chemother* 1998, 42(12): 3225.

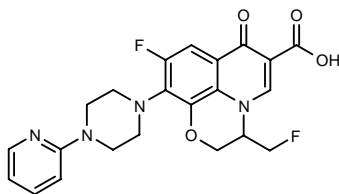
4. Vig, R. et al. *5-Alkyl-2-[(methylthiomethyl)thio]-6-(benzyl)-pyrimidin-4-(1H)-ones as potent non-nucleoside reverse transcriptase inhibitors of S-DABO series*. *Bioorg Med Chem Lett* 1998, 8(12): 1461.

*Identified compound **265590** Drug Data Report 1999, 021(02): 0158.

R-71762

274207

(±)-9-Fluoro-3-(fluoromethyl)-7-oxo-10-[4-(2-pyridinyl)-1-piperazinyl]-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid



C22 H20 F2 N4 O4; Mol wt: 442.4200

ACTION – Anti-HIV agent, a fluoroquinolone derivative shown to inhibit HIV-1-induced cytopathic effects in MT-4 cells at noncytotoxic concentrations (IC_{50} = 6.1 μ g/ml; CC_{50} > 25 μ g/ml). Compound also inhibited viral replication both in acutely (IC_{50} = 0.19 μ g/ml in CEM cells) and chronically HIV-1-infected cells (IC_{50} = 0.85 μ g/ml in MOLT-4 cells) at noncytotoxic concentrations (CC_{50} = 14 and > 30 μ g/ml, respectively). In contrast to other antibacterial quinolones such as ofloxacin, levofloxacin, ciprofloxacin, norfloxacin and enoxacin, only R-71762 showed anti-HIV-1 activity, although a narrower spectrum of antibacterial activity was observed for the title compound.

SOURCES – Sankyo; Ube.

REFERENCES

1. Komai, T. et al. (Sankyo Co., Ltd.) *Remedies of preventives for AIDS*. JP 97323932, WO 9727856.

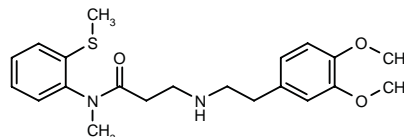
2. Uchiyama, H. et al. (Sankyo Co., Ltd.; Ube Industries, Ltd.) *TNF-production inhibitors*. JP 98130149.

3. Kashiwase, H. et al. *A new fluoroquinolone derivative exhibits inhibitory activity against human immunodeficiency virus type 1 replication*. *Chemotherapy* 1999, 45(1): 48.

TREATMENT OF PROTOZOAL DISEASES

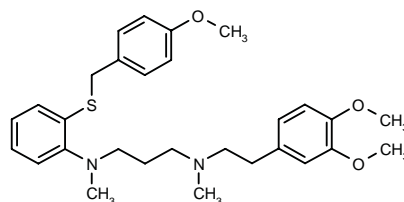
274755

3-[2-(3,4-Dimethoxyphenyl)ethylamino]-N-methyl-N-(2-methylsulfanyphenyl)propionamide



C21 H28 N2 O3 S; Mol wt: 388.5292

ACTION – Antiamebic agent for the treatment of dysentery with the advantage of being devoid of disturbing taste in man. It was active *in vivo* in rats infected with *Entamoeba histolytica*, with a potency higher than that of the reference compound tinidazole following oral administration. Another exemplified *ortho*-mercaptoaniline derivative is:



274756: C29 H38 N2 O3 S

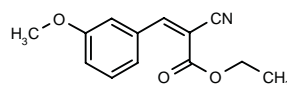
SOURCE – Akzo Nobel.

REFERENCES

1. Chaudhuri, S.K. and Poisson, C. (Akzo Nobel N.V.) *Novel ortho-mercaptoaniline cpds*. EP 903341.

274780

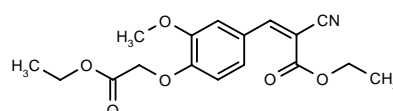
2-Cyano-3-(3-methoxyphenyl)-2(Z)-propenoic acid ethyl ester



C13 H13 N O3; Mol wt: 231.2497

Light yellow solid, m.p. 96-7 °C.

ACTION – Antileishmanial agent shown to inhibit *Leishmania donovani* *in vivo* by 77% in infected golden hamsters after 7-day treatment with 50 mg/kg p.o. or i.m. Another related compound from this series of α -cyano- β -substituted ethyl propenoates is:



274781: C17 H19 N O6

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

1. Tiwari, S. et al. *Synthesis and antileishmanial activity of alpha-cyano ethyl propenoates - A new class of antileishmanials*. *Arzneim-Forsch Drug Res* 1999, 49(2): 144.

LbelF4A

273924

Leishmania braziliensis homologue of initiation factor 4A

ACTION – *Leishmania braziliensis* antigen, a homologue of the eukaryotic initiation factor 4A (eIF4A) reported to be able to stimulate a Th1 immune response and IL-12 production, as demonstrated in several *in vitro* and *in vivo* tests, and thus potentially useful for the treatment of patients with leishmaniasis.

SOURCE – Corixa.

REFERENCES

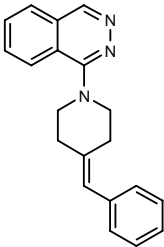
1. Reed, S.G. (Corixa Corp.) *Cpds. and methods for the stimulation and enhancement of protective immune responses and IL-12 production*. US 5876966.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

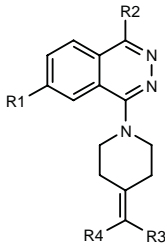
272791

1-[4-(Benzylidene)-1-piperidinyl]phthalazine



C20 H19 N3; Mol wt: 301.3911

ACTION – Tumor necrosis factor- α (TNF- α) production inhibitor, as demonstrated in lipopolysaccharide (LPS)-stimulated murine macrophages (IC_{50} = 2 μ M). A representative compound from a series of piperidinyl-phthalazine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
272792	H	H	2-thienyl	2-thienyl	C ₂₂ H ₁₉ N ₃ S ₂
272793	H	H	Ph	Ph	C ₂₆ H ₂₃ N ₃
272795	H	H	2-thienyl	H	C ₁₈ H ₁₇ N ₃ S
272796	NO2	Cl	Ph	H	C ₂₀ H ₁₇ ClN ₄ O ₂

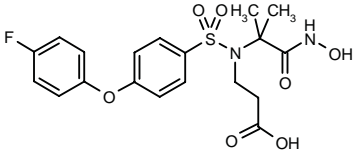
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Piperidinyl phthalazine derivs*. JP 99001481.

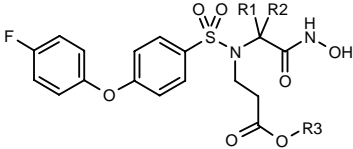
273618

N-[4-(4-Fluorophenoxy)phenylsulfonyl]-*N*-[1-(hydroxycarbamoyl)-1-methylethyl]- β -alanine



C19 H21 F N2 O7 S; Mol wt: 440.4459

ACTION – A selective inhibitor of human collagenase 3 (MMP-13; IC_{50} = 2.3-8 nM) with high selectivity relative to human collagenase 1 (MMP-1; IC_{50} = 2000-4800 nM), potentially useful for the treatment of a broad range of disorders including arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, bone resorption, atherosclerosis, multiple sclerosis and ocular angiogenesis. Other specifically claimed compounds from this series of aryloxyarylsulfonylamino hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	Formula
273619	H	cyclopentyl	Et	C ₂₄ H ₂₉ FN ₂ O ₇ S
273620	H	cyclopentyl	H	C ₂₂ H ₂₅ FN ₂ O ₇ S
273621	Me	Me	Et	C ₂₁ H ₂₅ FN ₂ O ₇ S

SOURCE – Pfizer.

REFERENCES

1. Robinson, R.P. (Pfizer Products Inc.) *Aryloxyarylsulfonylamino hydroxamic acid derivs*. WO 9907675.

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

1. Tiwari, S. et al. *Synthesis and antileishmanial activity of alpha-cyano ethyl propenoates - A new class of antileishmanials*. *Arzneim-Forsch Drug Res* 1999, 49(2): 144.

LbelF4A

273924

Leishmania braziliensis homologue of initiation factor 4A

ACTION – *Leishmania braziliensis* antigen, a homologue of the eukaryotic initiation factor 4A (eIF4A) reported to be able to stimulate a Th1 immune response and IL-12 production, as demonstrated in several *in vitro* and *in vivo* tests, and thus potentially useful for the treatment of patients with leishmaniasis.

SOURCE – Corixa.

REFERENCES

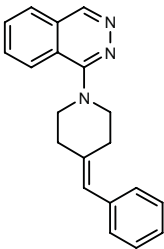
1. Reed, S.G. (Corixa Corp.) *Cpds. and methods for the stimulation and enhancement of protective immune responses and IL-12 production*. US 5876966.

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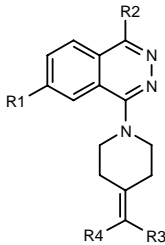
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Compound	R1	R2	R3	R4	Formula
272792	H	H	2-thienyl	2-thienyl	C ₂₂ H ₁₉ N ₃ S ₂
272793	H	H	Ph	Ph	C ₂₆ H ₂₃ N ₃
272795	H	H	2-thienyl	H	C ₁₈ H ₁₇ N ₃ S
272796	NO2	Cl	Ph	H	C ₂₀ H ₁₇ ClN ₄ O ₂

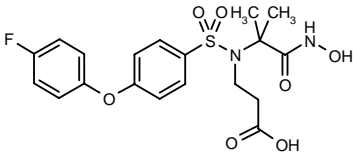
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujita, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Piperidinyl phthalazine derivs*. JP 99001481.

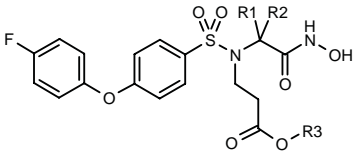
273618

N-[4-(4-Fluorophenoxy)phenylsulfonyl]-*N*-[1-(hydroxycarbamoyl)-1-methylethyl]- β -alanine



C19 H21 F N2 O7 S; Mol wt: 440.4459

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Compound	R1	R2	R3	Formula
273619	H	cyclopentyl	Et	C ₂₄ H ₂₉ FN ₂ O ₇ S
273620	H	cyclopentyl	H	C ₂₂ H ₂₅ FN ₂ O ₇ S
273621	Me	Me	Et	C ₂₁ H ₂₅ FN ₂ O ₇ S

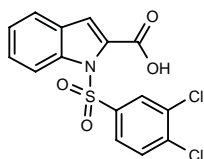
SOURCE – Pfizer.

REFERENCES

1. Robinson, R.P. (Pfizer Products Inc.) *Aryloxyarylsulfonylamino hydroxamic acid derivs*. WO 9907675.

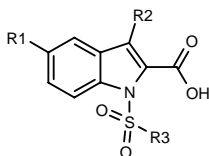
273624

1-(3,4-Dichlorophenylsulfonyl)-1*H*-indole-2-carboxylic acid



C15 H9 Cl2 N O4 S; Mol wt: 370.2111

ACTION – Monocyte chemoattractant protein-1 (MCP-1) receptor antagonist (IC_{50} = 10 μ M against human MCP-1 receptor B cloned in CHO cells) with potential in the treatment of rheumatoid arthritis, glomerulonephritis, lung fibrosis, restenosis, asthma, atherosclerosis, psoriasis, delayed-type hypersensitivity skin reactions, inflammatory bowel disease, multiple sclerosis, brain trauma, stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection. Within this series of indole derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
273625	Cl	H	6-Br-2-Naph	C ₁₉ H ₁₁ BrClNO ₄ S
273626	Cl	H	3-Cl-Ph	C ₁₅ H ₉ Cl ₂ NO ₄ S
273627	F	Br	3-CF ₃ -Ph	C ₁₆ H ₈ BrF ₄ NO ₄ S
273628	H	H	3-Cl-Ph	C ₁₅ H ₁₀ ClNO ₄ S

Compound	R1	R2	R3	Formula
273629	Cl	H	3,4-(Cl) ₂ -Ph	C ₁₅ H ₈ Cl ₃ NO ₄ S
273630	H	H	4,5-(Cl) ₂ -2-thienyl	C ₁₃ H ₇ Cl ₂ NO ₄ S ₂
273631	H	Br	3-CF ₃ -Ph	C ₁₆ H ₈ BrF ₃ NO ₄ S
273632	H	Cl	3-CF ₃ -Ph	C ₁₆ H ₉ ClF ₃ NO ₄ S

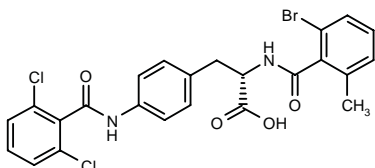
SOURCE – Zeneca (AstraZeneca).

REFERENCES

1. Barker, A.J. et al. (Zeneca Ltd.) *Indole derivs. as MCP-1 receptor antagonists*. WO 9907678.

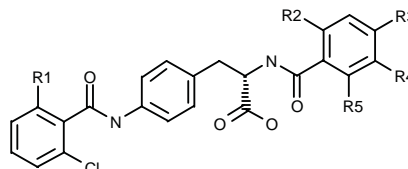
274345

2(*S*)-(2-Bromo-6-methylbenzamido)-3-[4-(2,6-dichloro-benzamido)phenyl]propionic acid

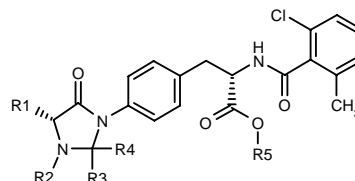


C24 H19 Br Cl2 N2 O4; Mol wt: 550.2341

ACTION – Agent for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease and multiple sclerosis that acts by inhibiting the interaction between vascular cell adhesion molecule-1 (VCAM-1) and the $\alpha_4\beta_1$ integrin receptor (also known as very late antigen-4 or VLA-4), giving IC_{50} values of 0.20 nM in an ELISA assay and of 9.3 nM in a cell-based assay. Other compounds from this series of *N*-alkanoylphenylalanine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
274347	Cl	Cl	H	H	Me	C ₂₄ H ₁₉ Cl ₃ N ₂ O ₄
274349	Cl	CF ₃	H	H	F	C ₂₄ H ₁₆ Cl ₂ F ₄ N ₂ O ₄
274352	Cl	Cl	H	Me	H	C ₂₄ H ₁₉ Cl ₃ N ₂ O ₄
274354	Cl	OMe	H	Br	H	C ₂₄ H ₁₉ BrCl ₂ N ₂ O ₅
274355	Cl	SMe	H	H	H	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₄ S
274357	Cl	Me	H	H	Et	C ₂₆ H ₂₄ Cl ₂ N ₂ O ₄
274359	Cl	Cl	SO ₂ Me	H	H	C ₂₄ H ₁₉ Cl ₃ N ₂ O ₆ S
274362	Me	Cl	H	H	Cl	C ₂₄ H ₁₉ Cl ₃ N ₂ O ₄



Compound	R1	R2	R3	R4	R5	Formula
274360	i-Pr	Me	-O-	Me	Me	C ₂₅ H ₂₈ ClN ₃ O ₅
274361	i-Bu	Ac	H	4-OH-Ph	H	C ₃₂ H ₃₄ ClN ₃ O ₆
274363	3-Pyr-CH ₂	Ac	H	Ph	H	C ₃₄ H ₃₁ ClN ₄ O ₅

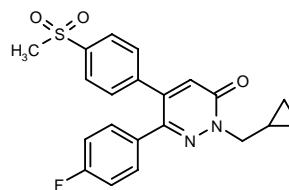
SOURCE – Roche.

REFERENCES

1. Chen, L. et al. (F. Hoffmann-La Roche AG) *N-Alkanoylphenylalanine derivs*. WO 9910312.

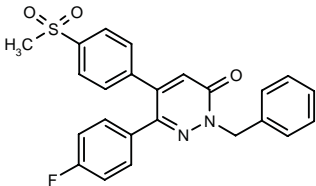
274506

2-(Cyclopropylmethyl)-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyridazin-3(2*H*)-one



C21 H19 F N2 O3 S; Mol wt: 398.4561

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2) with an IC₅₀ value of 250 nM for inhibition of human recombinant COX-2 versus only 24% inhibition of COX-1 at 100 μM. *In vivo*, it inhibited carrageenan-induced pleural inflammation in rats, giving 41% inhibition at 10 mg/kg p.o. Another compound from this series of pyridazinone derivatives is:



274507: C24 H19 F N2 O3 S

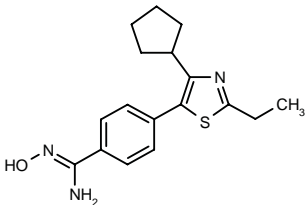
SOURCE – Abbott.

REFERENCES

1. Black, L.A. (Abbott Laboratories Inc.) *Prostaglandin endoperoxide H synthase biosynthesis inhibitors*. WO 9910332.

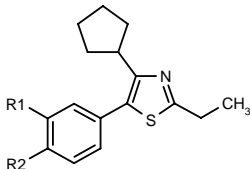
274679

4-(4-Cyclopentyl)-2-ethylthiazol-5-yl)-N²-hydroxybenzamidine



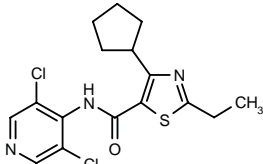
C17 H21 N3 O S; Mol wt: 315.4389

ACTION – Agent for the treatment of autoimmune and allergic disorders that acts by inhibiting the production of tumor necrosis factor-α (TNF-α) and interferon γ, as demonstrated *in vitro* in human peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS) or concanavalin A (IC₅₀ = 0.02 and 0.06 μM, respectively). *In vivo*, it inhibited by 89% the LPS-stimulated production of TNF-α in plasma of mice when given at 10 mg/kg p.o. In addition, compound was effective in a collagen-induced arthritis model in mice, reducing the arthritis score from 8.13 ± 0.68 in the control group to 3.40 ± 0.73 at 3 mg/kg/day p.o. x 52 days. Other exemplified compounds from this series of thiazole derivatives include the following:



Compound	R1	R2	Formula
274681	H	4,5-dihydro-2-oxazolyl	C ₁₉ H ₂₂ N ₂ OS
274684	Me	NH2	C ₁₇ H ₂₂ N ₂ S
274685	H	N(Me)CONHMe	C ₁₉ H ₂₅ N ₃ OS
274686	H	NHCON(Me)2	C ₁₉ H ₂₅ N ₃ OS
274687		-OCON(Me)-	C ₁₈ H ₂₀ N ₂ O ₂ S
274688	Me	NHCH2CONH2	C ₁₉ H ₂₅ N ₃ OS

Compound	R1	R2	Formula
274689	H	CON(Me)2	C ₁₉ H ₂₄ N ₂ OS
274690	NO2	CN	C ₁₇ H ₁₇ N ₃ O ₂ S
274691	Me	NHCO2Me	C ₁₉ H ₂₄ N ₂ O ₂ S
274692	H	C(NH2)=NOAc	C ₁₉ H ₂₃ N ₃ O ₂ S



274683: C16 H17 Cl2 N3 O S

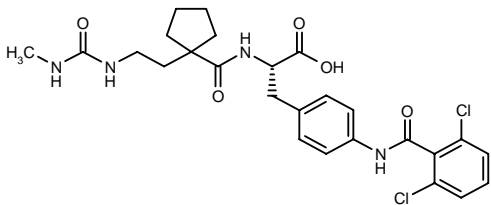
SOURCE – Japan Tobacco.

REFERENCES

1. Hashimoto, H. et al. (Japan Tobacco Inc.) *Thiazole cpds*. JP 99049762.

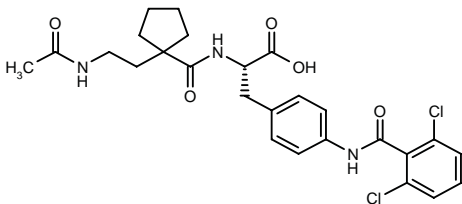
274744

3-[4-(2,6-Dichlorobenzamido)phenyl]-2(S)-[1-[2-(3-methylureido)ethyl]cyclopentylcarboxamido]propionic acid



C26 H30 Cl2 N4 O5; Mol wt: 549.4520

ACTION – Agent for the treatment of inflammatory conditions such as rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease, a cell adhesion inhibitor that blocks the interaction between α₄-containing integrins such as VLA-4 and VCAM-1 and cells expressing such receptors, giving IC₅₀ values of 0.27 nM in a VLA-4/VCAM-1 screening assay and of 5.7 nM in a cell-based assay. Another representative compound within this series of N-aryolphenylalanine derivatives is:



274745: C26 H29 Cl2 N3 O5

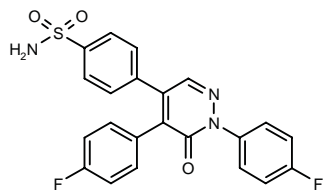
SOURCE – Roche.

REFERENCES

1. Chen, L. et al. (F. Hoffmann-La Roche AG) *N-Aryolphenylalanine derivs*. WO 9910313.

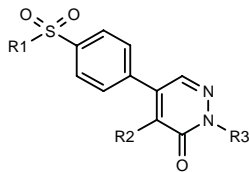
274833

4-[1,5-Bis(4-fluorophenyl)-6-oxo-1,6-dihydro-4-pyridazinyl]benzenesulfonamide



C22 H15 F2 N3 O3 S; Mol wt: 439.4405

ACTION – Antiinflammatory agent with markedly better gastrointestinal and renal tolerance than currently marketed nonsteroidal antiinflammatory drugs due to its selective inhibitory effect on cyclooxygenase type 2 (COX-2) activity. The IC₅₀ value against human recombinant COX-2 was 0.35 μM, whereas it only produced 40% inhibition of human recombinant COX-1 activity at a concentration of 10 μM, and 62% inhibition at 30 μM. Compound inhibited carrageenan-induced pleural inflammation in adrenalectomized rats (ED₅₀ = 3.4 mg/kg p.o.), as well as carrageenan-induced paw edema in rats (45.5% inhibition at 10 mg/kg p.o.), and carrageenan-induced air pouch prostaglandin biosynthesis (94% inhibition at 3 mg/kg p.o.). Within this wide series of arylpyridazinone derivatives, the following are also included:



Compound	R1	R2	R3	Formula
274834	NH2	4-Cl-Ph	CH2CF3	C ₁₈ H ₁₃ ClF ₃ N ₃ O ₃ S
274835	Me	4-F-Ph	3,4-(F)2-Ph	C ₂₃ H ₁₅ F ₃ N ₂ O ₃ S
274837	Me	i-BuCH2O	3-Cl-Ph	C ₂₂ H ₂₃ ClN ₂ O ₄ S
274838	Me	i-BuCH2O	4-F-Ph	C ₂₂ H ₂₃ FN ₂ O ₄ S
274839	NH2	t-BuCH2O	CH2CF3	C ₁₇ H ₂₀ F ₃ N ₃ O ₄ S

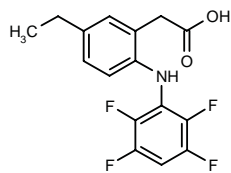
SOURCE – Abbott.

REFERENCES

1. Black, L.A. et al. (Abbott Laboratories Inc.) *Arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors*. WO 9910331.

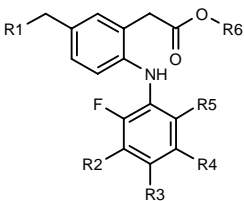
274890

2-[5-Ethyl-2-(2,3,5,6-tetrafluorophenylamino)phenyl]-acetic acid



C16 H13 F4 N O2; Mol wt: 327.2757

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.007 μM) with no significant COX-1 inhibition at 30 μM. *In vivo*, it inhibited COX-2-mediated PGE₂ production in the air pouch model with an ED₅₀ value in the range 0.2-0.6 mg/kg p.o. Analgesic activity was demonstrated in the paw pressure assay by an increase in pain threshold in the inflamed paw at 10 mg/kg p.o. Compound was free of gastric ulcerogenic effects at 100 mg/kg p.o. and did not show any effect on intestinal permeability at a dose of 30 mg/kg p.o. in rats. Within this series of 5-alkyl-2-arylaminophenylacetic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
274891	H	H	H	H	Cl	H	C ₁₅ H ₁₃ ClFNO ₂
274892	H	H	F	H	Cl	H	C ₁₅ H ₁₂ ClF ₂ NO ₂
274893	Me	F	H	F	F	CH2CO2H	C ₁₈ H ₁₅ F ₄ NO ₄

SOURCE – Novartis.

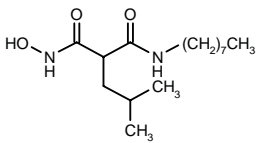
REFERENCES

1. Fujimoto, R.A. et al. (Novartis AG) *Certain 5-alkyl-2-arylaminophenylacetic acids and derivs*. WO 9911605.

274905

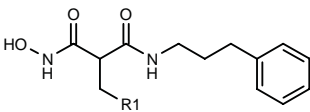
N¹-Hydroxy-2-isobutyl-N³-octylpropanediamide

N-Hydroxy-2-isobutyl-N'-octylmalonamide



C15 H30 N2 O3; Mol wt: 286.4130

ACTION – An inhibitor of matrix metalloproteinases (MMPs) with an IC₅₀ value of 0.30 μM for inhibition of human neutrophil collagenase (MMP-8). Potentially useful for the treatment of rheumatoid arthritis, systemic lupus erythematosus, corneal ulceration, osteoporosis, periodontitis and tumor invasion and metastasis. Other exemplified compounds from this series of malonic acid-based MMP inhibitors include the following:



Compound	R1	Formula
274906	i-Pr	C ₁₈ H ₂₄ N ₂ O ₃
274907	CH2Ph	C ₂₀ H ₂₄ N ₂ O ₃
274908	Ph	C ₁₉ H ₂₂ N ₂ O ₃

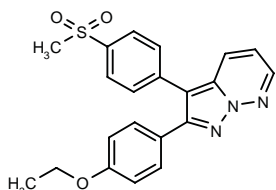
SOURCE – Roche Diagnostics.

REFERENCES

1. Grams, F. et al. (Roche Diagnostics GmbH) *Malonic acid based matrix metalloproteinase inhibitors*. EP 911319, WO 9911608.

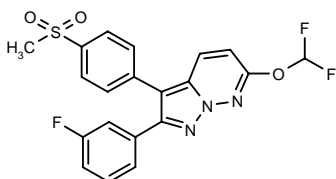
275282

2-(4-Ethoxyphenyl)-3-[4-(methylsulfonyl)phenyl]pyrazolo-[1,5-*b*]pyridazine



C21 H19 N3 O3 S; Mol wt: 393.4651

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated *in vitro* by IC₅₀ values of 3 and > 100,000 nM, respectively, against human COX-2 and COX-1 in stably transfected COS cells. Another specifically claimed compound from this series of 2,3-diarylpyrazolo[1,5-*b*]pyridazine derivatives is:



275283: C20 H14 F3 N3 O3 S

SOURCE – Glaxo Wellcome.

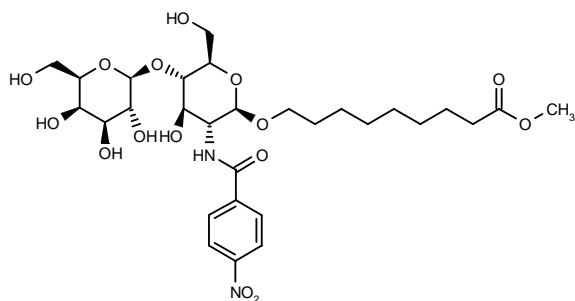
REFERENCES

1. Beswick, P. et al. (Glaxo Group Ltd.) *2,3-Diaryl-pyrazolo[1,5-*b*]pyridazines derivs., their preparation and their use as cyclooxygenase 2 (COX-2) inhibitors*. WO 9912930.

IMMUNOMODULATING AGENTS

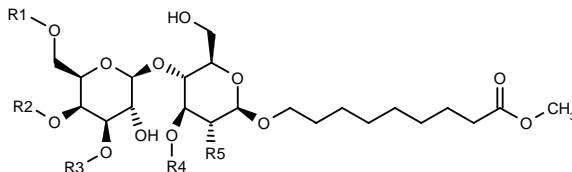
273414

9-[2-Deoxy-4-*O*-(β-D-galactopyranosyl)-2-(4-nitrobenz-amido)-β-D-glucopyranosyloxy]nonanoic acid methyl ester

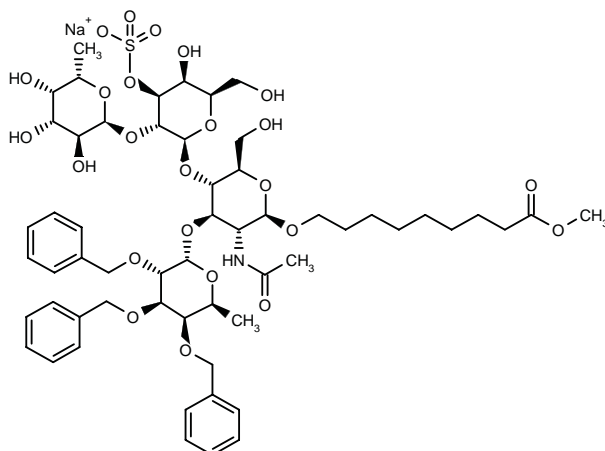


C29 H44 N2 O15; Mol wt: 660.6656

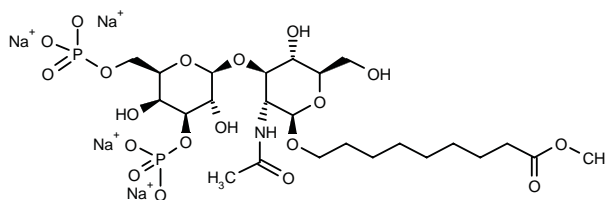
ACTION – Immunosuppressive agent proven active *in vivo* in the murine delayed-type hypersensitivity (DTH) test (48.4% reduction at 10 μg). Potentially useful for the treatment of psoriasis, asthma, dermatitis, rheumatoid arthritis, delayed-type hypersensitivity, inflammatory bowel disease, multiple sclerosis and viral and bacterial pneumonia. Other exemplified compounds from this series of oligosaccharide glycosides include the following:



Compound	R1	R2	R3	R4	R5	Formula
273415	H	PO3Na2	H	H	OH	C ₂₂ H ₃₉ Na ₂ O ₁₆ P
273416	SO3Na	SO3Na	SO3Na	α-L-fucosyl	NHAc	C ₃₀ H ₅₀ NNa ₃ O ₂₅ S ₃
273418	H	SO3Na	H	H	OH	C ₂₂ H ₃₉ NaO ₁₆ S



273417: C57 H80 N Na O24 S



273419: C24 H41 N Na4 O19 P2

SOURCE – Glycomed.

REFERENCES

1. Srivastava, O.P. et al. (Glycomed, Inc.) *Oligosaccharide glycosides having mammalian immunosuppressive and tolerogenic properties*. US 5874411.

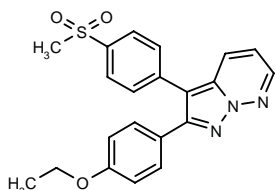
SOURCE – Roche Diagnostics.

REFERENCES

1. Grams, F. et al. (Roche Diagnostics GmbH) *Malonic acid based matrix metalloproteinase inhibitors*. EP 911319, WO 9911608.

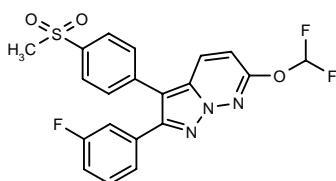
275282

2-(4-Ethoxyphenyl)-3-[4-(methylsulfonyl)phenyl]pyrazolo-[1,5-*b*]pyridazine



C21 H19 N3 O3 S; Mol wt: 393.4651

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated *in vitro* by IC₅₀ values of 3 and > 100,000 nM, respectively, against human COX-2 and COX-1 in stably transfected COS cells. Another specifically claimed compound from this series of 2,3-diarylpyrazolo[1,5-*b*]pyridazine derivatives is:



275283: C20 H14 F3 N3 O3 S

SOURCE – Glaxo Wellcome.

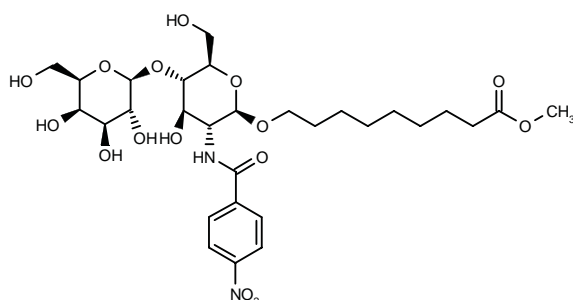
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1. Beswick, P. et al. (Glaxo Group Ltd.) *2,3-Diaryl-pyrazolo[1,5-*b*]pyridazines derivs., their preparation and their use as cyclooxygenase 2 (COX-2) inhibitors*. WO 9912930.

IMMUNOMODULATING AGENTS

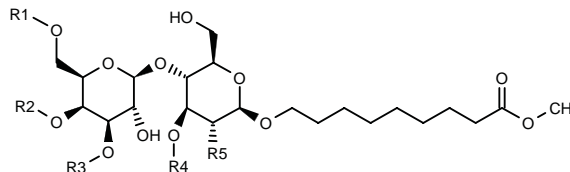
273414

9-[2-Deoxy-4-*O*-(β-D-galactopyranosyl)-2-(4-nitrobenz-amido)-β-D-glucopyranosyloxy]nonanoic acid methyl ester

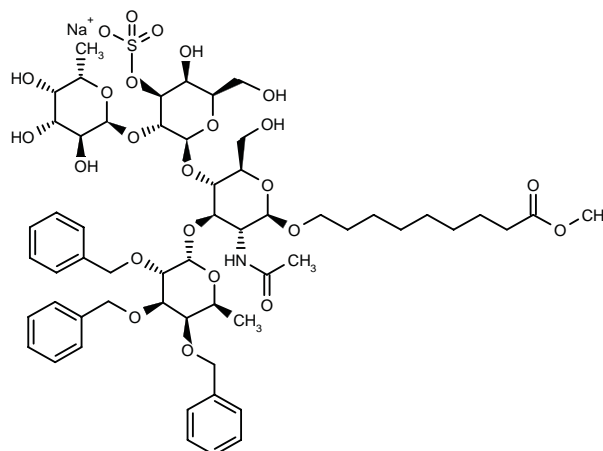


C29 H44 N2 O15; Mol wt: 660.6656

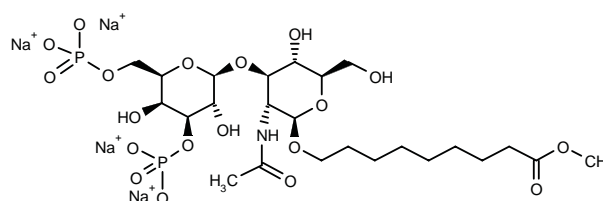
ACTION – Immunosuppressive agent proven active *in vivo* in the murine delayed-type hypersensitivity (DTH) test (48.4% reduction at 10 μg). Potentially useful for the treatment of psoriasis, asthma, dermatitis, rheumatoid arthritis, delayed-type hypersensitivity, inflammatory bowel disease, multiple sclerosis and viral and bacterial pneumonia. Other exemplified compounds from this series of oligosaccharide glycosides include the following:



Compound	R1	R2	R3	R4	R5	Formula
273415	H	PO3Na2	H	H	OH	C ₂₂ H ₃₉ Na ₂ O ₁₆ P
273416	SO3Na	SO3Na	SO3Na	α-L-fucosyl	NHAc	C ₃₀ H ₅₀ NNa ₃ O ₂₆ S ₃
273418	H	SO3Na	H	H	OH	C ₂₂ H ₃₉ NaO ₁₆ S



273417: C57 H80 N Na O24 S



273419: C24 H41 N Na4 O19 P2

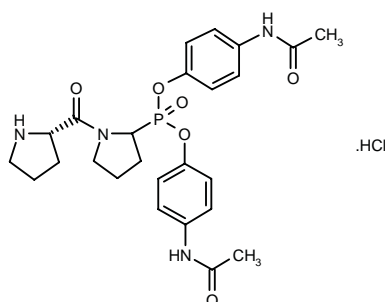
SOURCE – Glycomed.

REFERENCES

1. Srivastava, O.P. et al. (Glycomed, Inc.) *Oligosaccharide glycosides having mammalian immunosuppressive and tolerogenic properties*. US 5874411.

274730

1-(L-Prolyl)pyrrolidine-2-phosphonic acid bis(4-acetamidophenyl)ester hydrochloride



C₂₅ H₃₁ N₄ O₆ P . HCl; Mol wt: 550.9768

ACTION – Potent and irreversible inhibitor of dipeptidyl peptidase type IV (DPP IV; IC₅₀ = 0.4 μM) with high selectivity over other proteases such as prolyl endopeptidase, dipeptidyl peptidase II, membrane alanyl aminopeptidase and elastase. Compound showed no cytotoxicity in human peripheral blood mononuclear cells at concentrations up to 100 μM. Single i.v. injection of compound in rabbit decreased plasma DPP IV activity with an ED₅₀ of approximately 0.2 mg/kg.

Inhibitors of DPP IV have been reported to suppress T-cell proliferation, reduce antibody production and inhibit HIV-1 infection, and to be effective in animal models of arthritis and graft rejection.

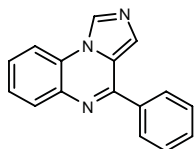
SOURCE – University of Antwerp, Antwerp (BE).

REFERENCES

1. Belyaev, A. et al. *Structure-activity relationship of diaryl phosphonate esters as potent irreversible dipeptidyl peptidase IV inhibitors*. J Med Chem 1999, 42(6): 1041.

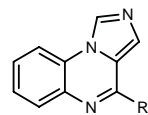
274773

4-Phenylimidazo[1,5-a]quinoxaline



C₁₆ H₁₁ N₃; Mol wt: 245.2839

ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment of transplant rejection, graft-versus-host disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, T-cell-mediated hypersensitivity disease, psoriasis, Guillain-Barre syndrome, cancer, dermatitis, allergy, asthma and ischemic or reperfusion injury. Other specifically claimed compounds from this series of imidazoquinoxaline derivatives include the following:



Compound	R1	Formula
274774	4-MeO-Ph	C ₁₇ H ₁₃ N ₃ O
274775	4-F-Ph	C ₁₆ H ₁₀ FN ₃
274776	2,6-(Me)2-Ph	C ₁₈ H ₁₅ N ₃
274777	2-Br-PhO	C ₁₆ H ₁₀ BrN ₃ O
274778	2-Br-PhS	C ₁₆ H ₁₀ BrN ₃ S
274779	2-Cl-6-Me-PhO	C ₁₇ H ₁₂ ClN ₃ O

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Barrish, J.C. and Spergel, S.H. (Bristol-Myers Squibb Co.) *Imidazoquinoxaline protein tyrosine kinase inhibitors*. WO 9910341.

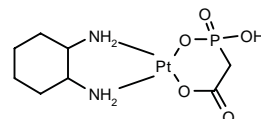
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

PADP

274705

(Cyclohexane-1,2-diamine)[2-phosphonoacetato-(2-)]platinum(II)



C₆ H₁₄ N₂ . C₂ H₃ O₅ P Pt; Mol wt: 447.2853

ACTION – Antineoplastic agent, a platinum complex with activity *in vitro* against several murine and human tumor cell lines (L1210, MCF-7, BT-20, DU-145, COLO-205, A-549 and SK-MEL-2), with IC₅₀ values of 50-55 μM. Compound produced 99.99% inhibition of clonogenic growth of L1210 cells. When given at a dose of 20 mg/kg to DBA/2 mice bearing leukemia L1210, compound increased life span by 200%. Currently undergoing phase I clinical trials.

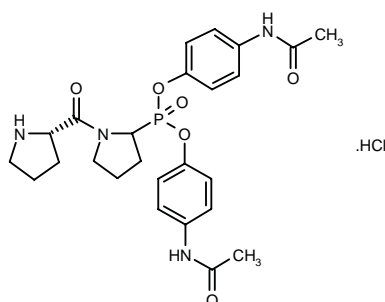
SOURCE – St. Paul Medical Center, Dallas, TX (US).

REFERENCES

1. Khan, A. et al. *Pre-clinical studies of a new compound phosphonoacetato-1,2-diaminocyclohexane platinum (II)*. Proc Amer Assoc Cancer Res 1999, 40: Abst 1950.

274730

1-(L-Prolyl)pyrrolidine-2-phosphonic acid bis(4-acetamidophenyl)ester hydrochloride



C₂₅ H₃₁ N₄ O₆ P . HCl; Mol wt: 550.9768

ACTION – Potent and irreversible inhibitor of dipeptidyl peptidase type IV (DPP IV; IC₅₀ = 0.4 μM) with high selectivity over other proteases such as prolyl endopeptidase, dipeptidyl peptidase II, membrane alanyl aminopeptidase and elastase. Compound showed no cytotoxicity in human peripheral blood mononuclear cells at concentrations up to 100 μM. Single i.v. injection of compound in rabbit decreased plasma DPP IV activity with an ED₅₀ of approximately 0.2 mg/kg.

Inhibitors of DPP IV have been reported to suppress T-cell proliferation, reduce antibody production and inhibit HIV-1 infection, and to be effective in animal models of arthritis and graft rejection.

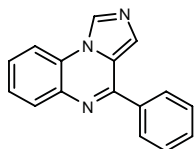
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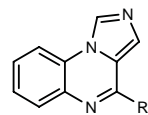
274773

4-Phenylimidazo[1,5-a]quinoxaline



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ACTION – An inhibitor of protein tyrosine kinases, especially Src family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment of transplant rejection, graft-versus-host disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, T-cell-mediated hypersensitivity disease, psoriasis, Guillain-Barre syndrome, cancer, dermatitis, allergy, asthma and ischemic or reperfusion injury. Other specifically claimed compounds from this series of imidazoquinoxaline derivatives include the following:



Compound	R1	Formula
274774	4-MeO-Ph	C ₁₇ H ₁₃ N ₃ O
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274776	2,6-(Me)2-Ph	C ₁₈ H ₁₅ N ₃
274777	2-Br-PhO	C ₁₆ H ₁₀ BrN ₃ O
274778	2-Br-PhS	C ₁₆ H ₁₀ BrN ₃ S
274779	2-Cl-6-Me-PhO	C ₁₇ H ₁₂ ClN ₃ O

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Barrish, J.C. and Spergel, S.H. (Bristol-Myers Squibb Co.) *Imidazoquinoxaline protein tyrosine kinase inhibitors*. WO 9910341.

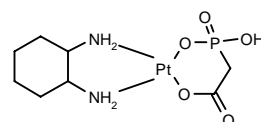
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

PADP

274705

(Cyclohexane-1,2-diamine)[2-phosphonoacetato-(2-)]platinum(II)



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SOURCE – St. Paul Medical Center, Dallas, TX (US).

REFERENCES

1. Khan, A. et al. *Pre-clinical studies of a new compound phosphonoacetato-1,2-diaminocyclohexane platinum (II)*. Proc Amer Assoc Cancer Res 1999, 40: Abst 1950.

TEMOZOLOMIDE

Rec INN: BAN

108485

8-Carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one

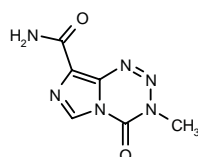
3-Methyl-4-oxo-3,4-dihydroimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide

CCRG-81045⁺

M&B-39831

NSC-362856

Sch-52365



C6 H6 N6 O2; Mol wt: 194.1534

ACTION – Antineoplastic agent, a triazene that undergoes rapid chemical conversion at physiological pH to the active alkylating agent monomethyl triazenoimidazole carboxamide (MTIC).

INDICATION – Treatment of glioblastoma multiforme progressing or recurring following standard therapy.

PRESENTATION – Capsules, 5, 20, 100 and 250 mg.

PROPRIETARY NAME – Temodal (GB).

SOURCES – Schering-Plough; licensed from Cancer Research Campaign Technology.

RECENT REFERENCES

1. Britten, C.D. et al. *A phase I safety and pharmacokinetics (PK) study of temozolomide in combination with cisplatin*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 442.
2. Brock, C.S. et al. *Response to temozolomide (TEM) in recurrent high grade gliomas (HGG) is related to tumour drug concentration*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 667.
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11. Hammond, L. et al. *Phase I and pharmacokinetic (PK) trial of sequences of BCNU and temozolomide (TMZ) in patients with solid neoplasms*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 441.

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42. *U.K. is country of first launch for Schering-Plough's oral alkylating agent* DailyDrugNews.com (Daily Essentials) 1999, March 12.

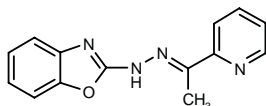
MONOGRAPH – Prous, J. et al. *Temozolomide.* Drugs Fut 1994, 19(8): 0746.

*Drug Data Rep 1985, 007(08): 0533.

ANTIMETABOLITES

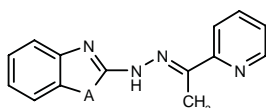
274480¹

1-(2-Pyridyl)-1-ethanone *N*-(2-benzoxazolyl)hydrazone



C₁₄ H₁₂ N₄ O; Mol wt: 252.2758

ACTION – Antineoplastic agent, an inhibitor of ribonucleotide reductase proven to inhibit the proliferation of several human tumor cells with IC₅₀ values ranging from 0.006 to 0.23 μM. Compound induced apoptosis in Burkitt's lymphoma cells and inhibited RNA synthesis. Other related 2-acetylpyridine hydrazones include the following:



Compound	A	Formula
274479 ^{1,2}	S	C ₁₄ H ₁₂ N ₄ S
274481 ¹	NH	C ₁₄ H ₁₃ N ₅

SOURCE – Universitaet Innsbruck, Innsbruck (AT).

REFERENCES

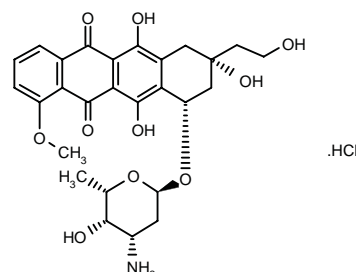
1. Easmon, J. et al. *Benzothiazolyl, benzoxazolyl, and benzimidazolyl hydrazones derived from 2-acetylpyridines: Synthesis and antitumor evaluation.* Proc Amer Assoc Cancer Res 1999, 40: Abst 1998.

2. Easmon, J. et al. *Thiazolyl and benzothiazolyl hydrazones derived from alpha-(N)-acetylpyridines and diazines: Synthesis, antiproliferative activity and CoMFA studies.* Eur J Med Chem 1997, 32: 397.

ANTIBIOTICS AND ALKALOIDS

273974

(8*R*,10*S*)-10-(3-Amino-2,3,6-trideoxy-α-L-galactopyranosyloxy)-6,8,11-trihydroxy-8-(2-hydroxyethyl)-1-methoxy-5,7,8,9,10,12-hexahydro-5,12-naphthacene-dione hydrochloride



C₂₇ H₃₁ N O₁₀ . HCl; Mol wt: 565.9998

ACTION – Antineoplastic agent, an anthracycline compound with the advantage over doxorubicin and daunorubicin that it is not metabolically converted to the cardiotoxic 13-dihydro form, as demonstrated *in vitro* in isolated rabbit cardiac muscle preparations, as well as in a chronic rabbit model at a dose of 1 mg/kg i.v. 2 times weekly for 8 weeks. It was as effective as doxorubicin in inhibiting the growth of human cancer cells, but showed less potency against different cancer cell lines such as HL-60 (IC₅₀ = 127 nM vs. 58 nM), P388 (IC₅₀ = 1980 nM vs. 269 nM), MCF7 (IC₅₀ = 72 nM vs. 17 nM) and MDA-MB-231 (IC₅₀ = 182 nM vs. 43 nM). It also produced less bone marrow toxicity than doxorubicin and was more effective than doxorubicin in prolonging survival in a murine P388 leukemia model. A representative compound within a series of 13-deoxyanthracycline derivatives.

SOURCE – Gem Pharmaceuticals.

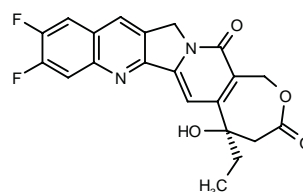
REFERENCES

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DNA-INTERCALATING DRUGS

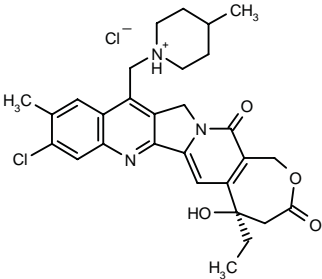
275176

(+)-5(*R*)-Ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,15-dione



C₂₁ H₁₆ F₂ N₂ O₄; Mol wt: 398.3634

ACTION – Antineoplastic, the pure (+)-enantiomer of a camptothecin analogue* with potent *in vitro* cytotoxicity against human colon adeno-carcinoma SW620, human ovarian adenocarcinoma OVCAR-5, human prostatic carcinoma PC-3 and DU 145, and human small cell lung adenocarcinoma NCI-H69 cells (IC₅₀ = 5, 8, 10, 1 and 0.3 nM, respectively). Another compound from this series of optically pure camptothecin analogues is:



275177: C₂₉ H₃₃ Cl₂ N₃ O₄

SOURCE – SCRAS.

REFERENCES

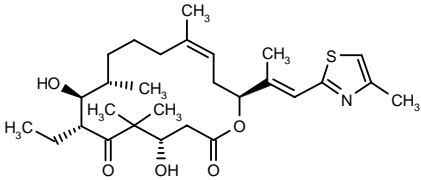
1. Cazaux, J.-B. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Optically pure camptothecin analogues, optically pure synthesis intermediate and method for preparing same.* WO 9911646.

*See **271570** Drug Data Report 1999, 021(03): 0265.

ANTIMITOTIC DRUGS

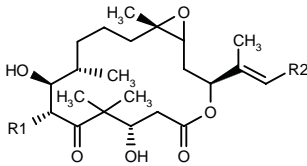
273937

(4*S*,7*R*,8*S*,9*S*,16*S*)-7-Ethyl-4,8-dihydroxy-5,5,9,13-tetramethyl-16-[(*E*)-1-methyl-2-(4-methylthiazol-2-yl)vinyl]oxacyclohexadec-13(*Z*)-ene-2,6-dione

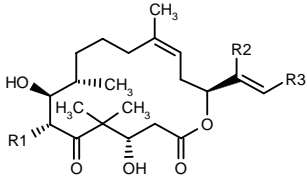


C₂₈ H₄₃ N O₅ S; Mol wt: 505.7157

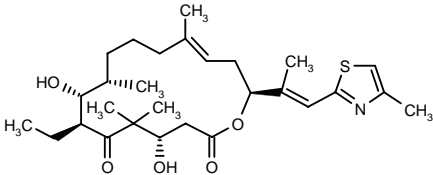
ACTION – Antineoplastic agent that interacts with tubulin by stabilizing formed microtubules. Compound is reported to be capable of influencing cell division in a phase-specific manner and is suitable for the treatment of malignant tumors such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. It is also reported to be suited for antiangiogenesis therapy and for the treatment of chronic inflammatory diseases such as psoriasis and arthritis. Other specifically claimed compounds from this series of epothilone derivatives include the following:



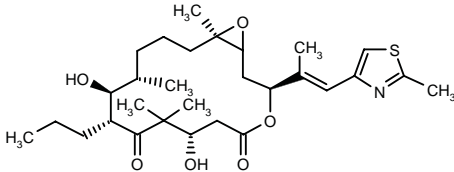
Compound	R1	R2	Formula
273939	Et	4-Me-2-thiazolyl	C ₂₈ H ₄₃ NO ₆ S
273942	CH ₂ Ph	2-Me-4-thiazolyl	C ₃₃ H ₄₅ NO ₆ S
273945	Me	4-Pyr	C ₂₈ H ₄₁ NO ₆



Compound	R1	R2	R3	Formula
273941	Me	H	3-Pyr	C ₂₇ H ₃₉ NO ₅
273943	CF ₂ CF ₃	Me	2-Me-4-thiazolyl	C ₂₈ H ₃₈ F ₅ NO ₅ S



273940: C₂₈ H₄₃ N O₅ S



273944: C₂₉ H₄₅ N O₆ S

SOURCE – Schering AG.

REFERENCES

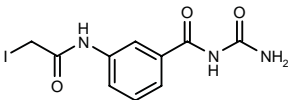
1. Klar, U. et al. (Schering AG) *New epothilone derivs., method for producing same and their pharmaceutical use.* WO 9907692.

3-IAABU

274451

N-[3-(Iodoacetamido)benzoyl]urea

N-(Aminocarbonyl)-3-(iodoacetamido)benzamide



C₁₀ H₁₀ I N₃ O₃; Mol wt: 347.1070

ACTION – Antineoplastic agent, an inhibitor of microtubule assembly, as demonstrated in tubulin systems with or without microtubule-associated proteins ($ID_{50} = 0.1$ and $1.2 \mu\text{M}$, respectively), that does not affect microtubule depolymerization. Compound showed *in vitro* antitumor activity against a variety of cell lines including leukemia ($ED_{50} = 0.015$ - $0.29 \mu\text{M}$) and solid tumor cells ($ED_{50} = 0.06$ - $0.92 \mu\text{M}$), and it was more selective than vinblastine and paclitaxel for malignant cells over normal human lymphocytes. Compound induced accumulation of tumor cells in M phase, followed by progression to apoptosis.

SOURCES – Cytoskeleton; Mount Sinai School of Medicine, New York, NY (US); New York University, New York, NY (US).

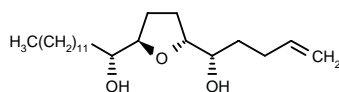
REFERENCES

1. Jiang, J.-D. et al. *Synthesis, cancericidal and antimicrotubule activities of 3-(haloacetamido)-benzoylureas*. *Anti-Cancer Drug Des* 1998, 13(7): 735.
2. Jiang, J.D. et al. *3-(Iodoacetamido)-benzoylurea: A novel cancericidal tubulin ligand that inhibits microtubule polymerization, phosphorylates bcl-2, and induces apoptosis in tumor cells*. *Cancer Res* 1998, 58(23): 5389.
3. Jiang, J.D. et al. *Molecular targets of 3-(iodoacetamido)-benzoylurea: A new cancericidal tubulin ligand*. *Proc Amer Assoc Cancer Res* 1999, 40: Abst 8.

DDE-313

273748

1(*S*)-[5(*R*)-[1(*R*)-Hydroxytridecyl]tetrahydrofuran-2(*R*)-yl]-4-penten-1-ol



C22 H42 O3; Mol wt: 354.5708

ACTION – Antineoplastic agent, an epoxy tetrahydrofuran-containing compound with potent tubulin-depolymerizing activity.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

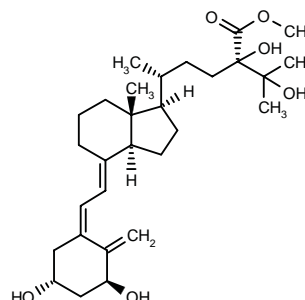
REFERENCES

1. Jan, S.-T. et al. *An epoxy-THF containing compound with potent tubulin depolymerizing activity as a novel anti-cancer agent*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 024.

HORMONAL AGENTS

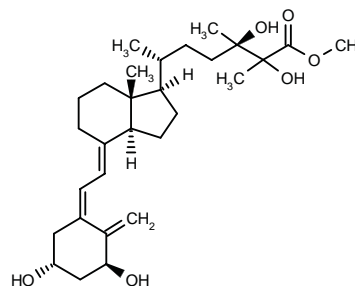
274632

1 α ,24(*S*),25-Trihydroxyvitamin D₃-24-carboxylic acid methyl ester



C29 H46 O6; Mol wt: 490.6764

ACTION – Differentiation-inducing agent, a vitamin D₃ analogue with comparable potency to 1,25-dihydroxyvitamin D₃ in inducing differentiation of HL-60 cells (40 and 40%, respectively, at $0.01 \mu\text{M}$; 65 and 60%, respectively, at 0.1 mcM). Another compound from this series of vitamin D₃ analogues is:



274633: C29 H46 O6

SOURCES – Nisshin Flour Milling; Teikoku Hormone.

REFERENCES

1. Honma, S. et al. (Teikoku Hormone Manufacturing Co., Ltd.; Nisshin Flour Milling Co., Ltd.) *Active vitamin D derivs*. JP 99049747.

CANCER IMMUNOTHERAPY

ALVAC-CEA

274569

Recombinant canarypox virus that contains the entire human carcinoembryonic antigen (CEA) gene inserted into its genome

ACTION – Vaccine for cancer immunotherapy, a recombinant canarypox virus with the entire human carcinoembryonic antigen (CEA) gene inserted into its genome. In a phase I clinical trial, patients with advanced CEA-expressing carcinoma who were administered the recombinant vaccine (3 times at 28-day intervals i.m.) showed CEA-specific cytolytic T-lymphocyte (CTL) responses. Vaccine was well tolerated at all dose levels and no significant toxicity was attributed to treatment.

SOURCE – National Cancer Institute, Bethesda, MD (US).

REFERENCES

1. Hodge, J.W. et al. *Diversified prime and boost protocols using recombinant vaccinia virus and recombinant non-replicating avian pox virus to enhance T-cell immunity and antitumor responses.* Vaccine 1997, 15(6-7): 759.

2. Marshall, J.L. et al. *Phase I study in cancer patients of a replication-defective avipox recombinant vaccine that expresses human carcinoembryonic antigen.* J Clin Oncol 1999, 17(1): 332.

3. Marshall, J.L. et al. *Phase I/II trial of vaccinia-CEA (V) and ALVAC-CEA (A) in patients with advanced CEA-bearing tumors.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1690.

4. Zhu, M.Z. et al. *Specific T-cell responses to human carcinoembryonic antigen from patients immunized with recombinant canarypox (ALVAC)-CEA vaccine.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2797.

GM2-KLH/QS-21

231576

Therapeutic cancer vaccine based on the ganglioside GM2 (molecule composed of carbohydrates and lipids present in 95% of melanoma cells) coupled to the carrier protein keyhole limpet hemocyanin (KLH) and formulated with QS-21 adjuvant

BMS-248479
GMK vaccine

ACTION – Cancer vaccine for the treatment of malignant melanoma that contains the ganglioside GM2, a tumor-associated glycolipid antigen overexpressed on the surface of human melanomas, linked to the carrier protein keyhole limpet hemocyanin (KLH) and adjuvanted with QS-21. Phase II studies in malignant melanoma patients immunized at intervals of 1, 2, 3, 4, 12, 24 and 36 weeks with vaccine containing 1, 3, 10 and 30 µg GM2 demonstrated that it induced IgM and IgG (predominantly IgG₁ and IgG₃ subtype) anti-GM2 antibodies. The serum of the 52 patients completing the study showed potent and specific complement-mediated cytotoxicity as well as specific cell-killing activity. The vaccine was generally well tolerated by all patients, with no serious toxicities reported. It is currently being evaluated in large-scale phase II clinical trials in patients at high risk for relapse of malignant melanoma.

SOURCES – Bristol-Myers Squibb; Memorial Sloan-Kettering Cancer Center, New York, NY (US); Progenics.

REFERENCES

1. Chapman, P.B. et al. *Eastern Cooperative Oncology Group phase II randomized adjuvant trial of GM2-KLH + QS21 (GMK) vaccine ± high dose interferon-α2b (HD IFN) in melanoma (MEL).* Proc Amer Soc Clin Oncol 1999, 18: Abst 2078.

2. Eggermont, A.M.M. *The current EORTC Melanoma Cooperative Group adjuvant trial programme on malignant melanoma: Prognosis versus efficacy, toxicity and costs.* Melanoma Res 1997, 7(Suppl. 2): S127.

3. Gilewski, T. et al. *Vaccination of high risk breast cancer patients (pts) lacking identifiable disease with GM2-keyhole limpet hemocyanin (KLH) conjugate plus QS-21.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1694.

4. Helling, F. et al. *Phase II clinical trial of GM2-KLH/QS-21 vaccine in patients with malignant melanoma.* Proc Amer Assoc Cancer Res 1996, 37: Abst 3354.

5. Israel, R.J. et al. *Mechanisms of cytotoxic antibodies induced by the ganglioside conjugate vaccine GM2-KLH/QS-21 in melanoma patients.* Proc Amer Assoc Cancer Res 1999, 40: Abst 1705.

6. Israel, R.J. et al. *Phase I/II dose-ranging clinical trials of the ganglioside conjugate cancer vaccines GM2-KLH/QS-21 (GMK) and GM2-KLH/GD2-KLH/QS-21 (MGV).* Proc Amer Soc Clin Oncol 1999, 18: Abst 1675.

7. Israel, R.J. et al. *Phase II and III clinical development of GM2-KLH/QS21 vaccine for melanoma.* Melanoma Res 1997, 7(Suppl. 1): Abst 182.

8. Israel, R.J. et al. *Phase II clinical trial of GM2-KLH/QS-21 (GMK) vaccine in patients with malignant melanoma.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 322.

9. Slovin, S. et al. *Ganglioside vaccines in relapsed prostate cancer (PC): Experience with GM2-KLH conjugate plus the immunologic adjuvant, QS-21 - A trial comparing QS21 doses.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1214.

10. Bristol-Myers Squibb and Progenics Pharmaceuticals announce licensing agreement for cancer vaccines. Progenics Pharmaceuticals, Inc. Press Release 1997, July 16.

11. *Company Profile: Progenics.* DailyDrugNews.com (Daily Essentials) 1997, Nov 28.

12. *Progenics Pharmaceuticals licenses clinically advanced cancer vaccine from Memorial Sloan-Kettering.* Progenics Pharmaceuticals, Inc. Press Release 1995, Dec 15.

13. *Progenics Pharmaceuticals' MGV cancer vaccine shows promising results in phase I/II clinical trials and animal studies. Results presented at AACR Annual Meeting.* Progenics Pharmaceuticals, Inc. Press Release 1998, March 31.

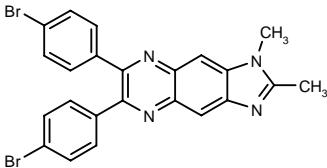
14. *Progenics receives payment for cancer vaccine milestone.* DailyDrugNews.com (Daily Essentials) 1998, June 24.

15. ProGen Industries Ltd. *Company Profile* 1995, November.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

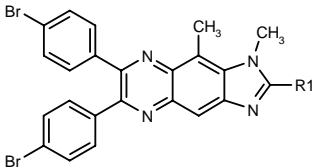
273708

6,7-Bis(4-bromophenyl)-1,2-dimethyl-1H-imidazo[4,5-g]-quinoxaline



C23 H16 Br2 N4; Mol wt: 508.2154

ACTION – Agent for the treatment of cancer, arthritis, diabetic retinopathy, restenosis, hepatic cirrhosis, atherosclerosis, angiogenesis, glomerulonephritis, diabetic nephropathy, transplant rejection, autoimmune diseases, diabetes and hyperimmune disorders that acts by modulating the activity of both receptor and nonreceptor protein tyrosine kinases. Other exemplified compounds from this series of tricyclic quinoxaline derivatives include the following:



Compound	R1	Formula
273709	Me	C ₂₄ H ₁₈ Br ₂ N ₄
273710	NH2	C ₂₃ H ₁₇ Br ₂ N ₅
273711	NHMe	C ₂₄ H ₁₉ Br ₂ N ₅

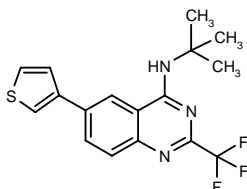
SOURCE – Sugen.

REFERENCES

1. Tang, P.C. and McMahon, G. (Sugen, Inc.) *Tricyclic quinoxaline derivs. as protein tyrosine kinase inhibitors*. WO 9907701.

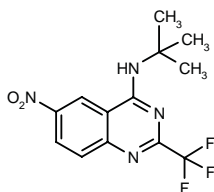
273754

4-*tert*-Butylamino-6-(3-thienyl)-2-(trifluoromethyl)-quinazoline



C17 H16 F3 N3 S; Mol wt: 351.3944

ACTION – Potential antineoplastic agent, a cyclin-dependent kinase (CDK) inhibitor (IC_{50} = 3.55 and 0.54 μ M against CDK4/D and CDK2/E, respectively). Another 2,6-disubstituted-4-aminoquinazoline compound is:



273755: C13 H13 F3 N4 O2

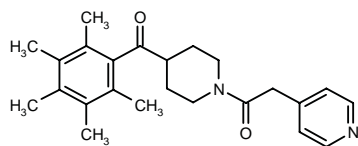
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Sielecki, T.M. et al. *Quinoxalines as cyclin-dependent kinase inhibitors: SAR of the R2 and R6 position*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MED1 055.

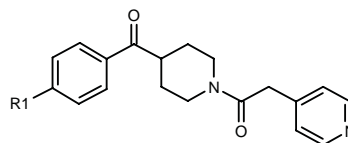
273969

1-[4-(2,3,4,5,6-Pentamethylbenzoyl)-1-piperidiny]-2-(4-pyridinyl)-1-ethanone

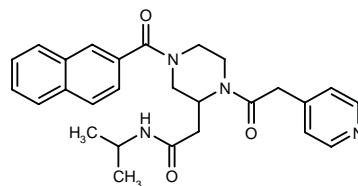


C24 H30 N2 O2; Mol wt: 378.5130

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} = 12.1 μ M). Other compounds from this series of carbonyl piperazinyl and piperidinyl derivatives include the following:



Compound	R1	Formula
273971	F	C ₁₉ H ₁₉ FN ₂ O ₂
273972	Cl	C ₁₉ H ₁₉ ClN ₂ O ₂
273973	H	C ₁₉ H ₂₀ N ₂ O ₂



273970: C27 H30 N4 O3

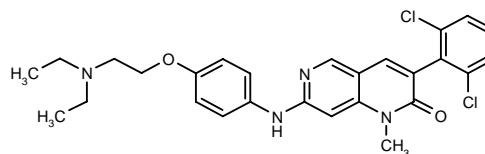
SOURCES – Pharmacopeia; Schering-Plough.

REFERENCES

1. Doll, R.J. et al. (Schering Corp.;Pharmacopeia, Inc.) *Carbonyl piperazinyl and piperidinyl cpds*. US 5880128.

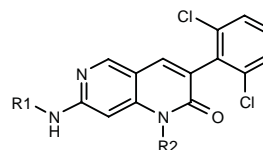
273983

3-(2,6-Dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]-phenylamino]-1-methyl-1,6-naphthyridin-2(1*H*)-one



C27 H28 Cl2 N4 O2; Mol wt: 511.4502

ACTION – Agent for the treatment or prevention of cancer, atherosclerosis, restenosis and psoriasis, a potent inhibitor of tyrosine kinases such as s-src (IC_{50} = 0.08 μ M), fibroblast growth factor (FGF) receptor tyrosine kinase (IC_{50} = 0.06 μ M), platelet-derived growth factor (PDGF) receptor tyrosine kinase (IC_{50} = 0.09 μ M) and epidermal growth factor (EGF) receptor tyrosine kinase (IC_{50} = 0.59 μ M), with selectivity over protein kinase C (PKC; IC_{50} > 50 μ M) and the intracellular kinase domains of insulin receptor (INSr; IC_{50} > 50 μ M). In addition, it was found to inhibit PDGF-stimulated receptor autophosphorylation in rat aorta smooth muscle cells with an IC_{50} value of 0.23 μ M. Compound inhibited the growth of human colon carcinoma HCT-8, SW-620 and HT-29 cells with respective IC_{50} values of 2.8, 6.7 and 0.8 μ M. Within this series of naphthyridinone derivatives, the following are also included:



Compound	R1	R2	Formula
273986	(CH ₂) ₄ N(Et) ₂	H	C ₂₂ H ₂₆ Cl ₂ N ₄ O
273987	4-Me-1-Piz-(CH ₂) ₃	Me	C ₂₃ H ₂₇ Cl ₂ N ₅ O
273991	2-[4-(4-Me-1-Piz-CH ₂ -CH ₂ O)-PhNH]-4-Pyr	Me	C ₃₃ H ₃₃ Cl ₂ N ₇ O ₂

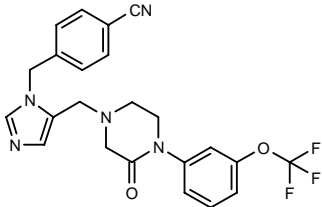
SOURCE – Warner-Lambert.

REFERENCES

1. Barvian, M.R. et al. (Warner-Lambert Co.) *Naphthyridinones for inhibiting protein tyrosine kinase and cell cycle kinase mediated cellular proliferation*. WO 9909030.

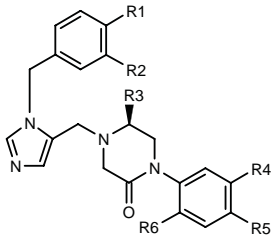
274254

4-[5-[3-Oxo-4-[3-(trifluoromethoxy)phenyl]-1-piperazinyl-methyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C23 H20 F3 N5 O2; Mol wt: 455.4380

ACTION – Antineoplastic agent, an inhibitor of protein prenyltransferases such as protein farnesyltransferase and protein geranylgeranyltransferase type I, and of the prenylation of the oncogene protein Ras. Other specifically claimed compounds within this series of substituted imidazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
274255	CN	H	H	Me	H	Me	C ₂₄ H ₂₅ N ₅ O
274256	CN	OMe	H	Cl	H	H	C ₂₃ H ₂₂ ClN ₅ O ₂
274257	CN	H	CH ₂ OCH ₂ Ph	Cl	H	H	C ₃₀ H ₂₈ ClN ₅ O ₂
274258	CN	H	H	SMe	H	H	C ₂₃ H ₂₃ N ₅ OS
274259	CN	H	H	Cl	F	H	C ₂₂ H ₁₉ ClFN ₅ O
274260	NO ₂	H	H	Cl	H	H	C ₂₁ H ₂₀ ClN ₅ O ₃
274261	CN	H	H	F	F	H	C ₂₂ H ₁₉ F ₂ N ₅ O

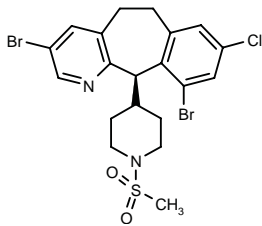
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 9909985.

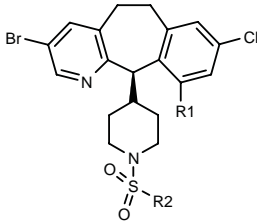
274321

3,10-Dibromo-8-chloro-11(*R*)-[1-(methylsulfonyl)piperidin-4-yl]-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine



C20 H21 Br2 Cl N2 O2 S; Mol wt: 548.7249

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC₅₀ = 0.0070 μM). Other compounds from this series of tricyclic sulfonamide derivatives include the following:



Compound	R1	R2	Formula
274322	Cl	Me	C ₂₀ H ₂₁ BrCl ₂ N ₂ O ₂ S
274323	Cl	NH ₂	C ₁₉ H ₂₀ BrCl ₂ N ₃ O ₂ S
274324	Br	Et	C ₂₁ H ₂₃ Br ₂ ClN ₂ O ₂ S
274325	Br	Pr	C ₂₂ H ₂₅ Br ₂ ClN ₂ O ₂ S
274326	Br	CF ₃	C ₂₀ H ₁₈ Br ₂ ClF ₃ N ₂ O ₂ S
274327	Br	CH ₂ CF ₃	C ₂₁ H ₂₀ Br ₂ ClF ₃ N ₂ O ₂ S
274328	Br	vinyl	C ₂₁ H ₂₁ Br ₂ ClN ₂ O ₂ S
274329	Br	1-Me-4-imidazolyl	C ₂₃ H ₂₃ Br ₂ ClN ₄ O ₂ S

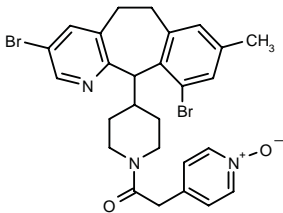
SOURCE – Schering-Plough.

REFERENCES

1. Njoroge, F.G. et al. (Schering Corp.) *Novel tricyclic sulfonamide inhibitors of farnesyl protein transferase*. WO 9857949.

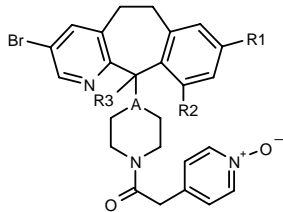
274330

(+)-1-[4-(3,10-Dibromo-8-methyl-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)piperidin-1-yl]-2-(1-oxidopyridin-4-yl)ethanone

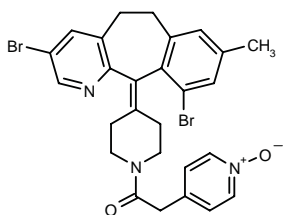


C27 H27 Br2 N3 O2; Mol wt: 585.3373

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC₅₀ = 0.0012 μM). Other exemplified compounds within this series of tricyclic derivatives include the following:



Compound	R1	R2	R3	A	Isomer	Formula
274331	Me	OMe	H	CH	racemic	C ₂₈ H ₃₀ BrN ₃ O ₃
274332	Me	OMe	H	N	(-)	C ₂₇ H ₂₉ BrN ₄ O ₃
274333	Me	Br	H	N	racemic	C ₂₆ H ₂₆ Br ₂ N ₄ O ₂
274334	Br	Me	H	N	(+)	C ₂₆ H ₂₆ Br ₂ N ₄ O ₂
274335	Me	OMe	H	CH	(+)	C ₂₈ H ₃₀ BrN ₃ O ₃
274336	Me	Br	OH	CH	(-)	C ₂₇ H ₂₇ Br ₂ N ₃ O ₃



274337: C₂₇ H₂₅ Br₂ N₃ O₂

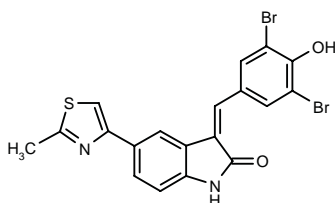
SOURCE – Schering-Plough.

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1. Afonso, A. et al. (Schering Corp.) *Novel phenyl-substd. tricyclic inhibitors of farnesyl-protein transferase*. WO 9857950.

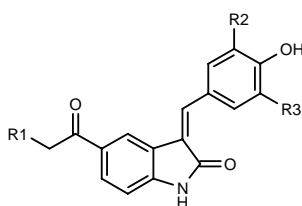
274490

3-[(Z)-3,5-Dibromo-4-hydroxybenzylidene]-5-(2-methylthiazol-4-yl)-2,3-dihydro-1*H*-indol-2-one



C₁₉ H₁₂ Br₂ N₂ O₂ S; Mol wt: 492.1898

ACTION – Antineoplastic agent, a selective inhibitor of the serine/threonine kinase cRaf1 (IC₅₀ < 1.0 μM) proven to exert *in vitro* cytotoxicity against human colon carcinoma SW620, human pancreatic carcinoma MIA PACA, human breast carcinoma MDA-MB-468 and human colon carcinoma HT-29 cells, with IC₅₀ values in the range 0.50-5 μM. *In vivo*, it produced 50% inhibition of tumor growth in mice bearing HT-29 xenografts at 5 mg/kg. A representative compound from a series of benzylidene-1,3-dihydroindol-2-one derivatives, wherein the following are also included:



Compound	R1	R2=R3	Formula
274491	Cl	Br	C ₁₇ H ₁₀ Br ₂ ClNO ₃
274492	N(Et) ₂	Cl	C ₂₁ H ₂₀ Cl ₂ N ₂ O ₃

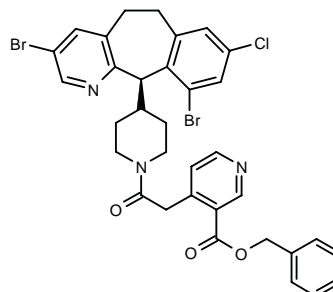
SOURCE – Glaxo Wellcome.

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1. McNutt, R.W. Jr. et al. (Glaxo Group Ltd.) *Benzylidene-1,3-dihydro-indol-2-one derivs. as receptor tyrosine kinase inhibitors, particularly of Raf kinases*. WO 9910325.

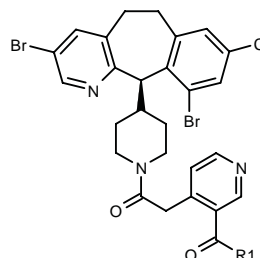
274593

(+)-4-[2-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-2-oxoethyl]pyridine-3-carboxylic acid benzyl ester



C₃₄ H₃₀ Br₂ Cl N₃ O₃; Mol wt: 723.8900

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other exemplified tricyclic compounds include the following:



Compound	R1	Formula
274594	OH	C ₂₇ H ₂₄ Br ₂ ClN ₃ O ₃
274595	NH ₂	C ₂₇ H ₂₅ Br ₂ ClN ₄ O ₂
274596	OMe	C ₂₈ H ₂₆ Br ₂ ClN ₃ O ₃

SOURCE – Schering-Plough.

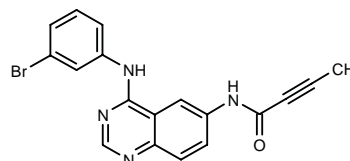
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CL-387785*

264472

N-[4-(3-Bromophenylamino)quinazolin-6-yl]-2-butanamide



C₁₈ H₁₃ Br N₄ O; Mol wt: 381.2317

ACTION – Antineoplastic agent, a selective and irreversible inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase-mediated signal transduction with IC_{50} values of 370 pM and 997 nM for inhibition of EGF receptor and c-erbB-2 kinase activity, respectively. Compound blocked EGF receptor ($IC_{50} = 5$ nM) and c-erbB-2 phosphorylation ($IC_{50} = 1$ μ M) in cells and inhibited the proliferation ($IC_{50} = 31$ -125 nM), principally in a cytostatic manner, of cells overexpressing EGF receptor or c-erbB-2. In nude mice bearing human epidermoid adenocarcinoma A-431 tumors, compound (20 mg/kg/day x 10 days p.o.) inhibited tumor growth and EGF receptor phosphorylation in tumors.

SOURCE – American Home Products.

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1. Wissner, A. et al. (American Cyanamid Co.) 4-Aminoquinazoline EGFR inhibitors. EP 787722, US 5760041.

2. Discatani, C.M. et al. Inhibition of epidermal growth factor receptor tyrosine kinase family members by the covalent antagonist CL-387.785. Proc Amer Assoc Cancer Res 1999, 40: Abst 4817.

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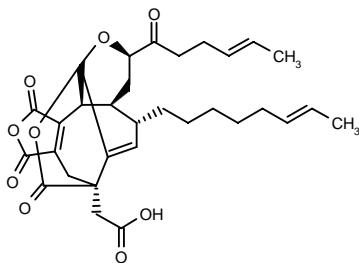
*Identified compound **264472** Drug Data Report 1998, 020(07): 0630.

CP-263114

256691

(-)-2-[14-[4(*E*)-Hexenoyl]-18-[6(*E*)-octenyl]-3,7,9-trioxo-2,8,15-trioxapentacyclo[10.3.3.0^{1,11}.0^{4,16}.0^{6,10}]octadeca-6(10),16-dien-4-yl]acetic acid

(-)-(5*R**,7*aR**,9*R**,11*S**,11*aS**,12*S**)-12-[6(*E*)-Octenyl]-1,3,6-trioxo-9-[1-oxo-4(*E*)-hexenyl]-1,4,9,10,11,11*a*-hexahydro-11,5,7*a*-[2]propen[1]yl[3]ylidene-3*H*,7*aH*-furo[3,4-*d*]pyrano[2,3-*b*]oxocin-5(6*H*)-acetic acid



C31 H36 O9; Mol wt: 552.6164

ACTION – Protein farnesyltransferase inhibitor ($IC_{50} = 20$ μ M against rat brain enzyme) produced by an undefined fungus. Compound inhibited squalene synthase from rat hepatic microsomes with an IC_{50} of 160 μ M, indicating an 8-fold specificity for protein farnesyltransferase over squalene synthase.

SOURCE – Pfizer.

REFERENCES

1. Bio, M.M. and Leighton, J.L. An approach to the synthesis of CP-263,114: A remarkably facile silyloxy-cope rearrangement. J Am Chem Soc 1999, 121(4): 890.

2. Corbett, R.M. et al. Synthesis of CP-263,114 and CP-225,917: Novel bioactive fungal metabolites. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 036.

3. Critchley, T.J. et al. Synthetic studies towards CP-225,917 and CP-263,114. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 372.

4. Chen, C. et al. Stereospecific synthesis of the CP-263,114 core structure. J Am Chem Soc 1998, 120(41): 10784.

5. Dabrah, T.T. et al. CP-225,917 and CP-263,114, novel ras farnesylation inhibitors from an unidentified fungus. 1. Taxonomy, fermentation, isolation, and biochemical properties. J Antibiot 1997, 50(1): 1.

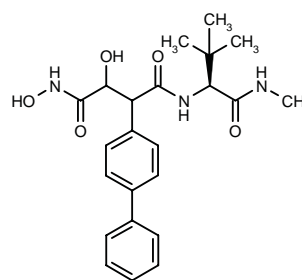
6. Dabrah, T.T. et al. CP-225,917 and CP-263,114: Novel ras farnesylation inhibitors from an unidentified fungus. 2. Structure elucidation. J Am Chem Soc 1997, 119(7): 1594.

7. Waizumi, N. et al. Synthetic studies on CP-225,917 and CP-263,114. Tetrahedron Lett 1998, 39(33): 6015.

ANGIOGENESIS INHIBITORS

273165

2-(Biphenyl-4-yl)-*N*¹-[2,2-dimethyl-1(*S*)-(N-methylcarbamoyl)propyl]-*N*⁴,3-dihydroxysuccinamide



C23 H29 N3 O5; Mol wt: 427.4981

ACTION – An analogue of marimastat reported to possess an improved side effect profile by virtue of its selective affinity for gelatinases relative to other matrix metalloproteinases (MMPs) such as MMP-1 (fibroblast collagenase) as compared to marimastat, which is a broad-spectrum MMP inhibitor. A representative compound from a series of 3-arylsuccinamido hydroxamic acid derivatives with potential for tumor metastasis and invasion.

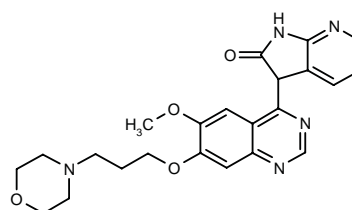
SOURCE – Roche Diagnostics.

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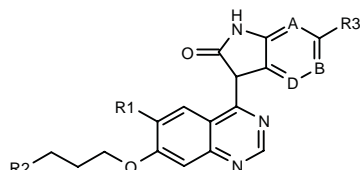
274813

3-[6-Methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolin-yl]-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-2-one



C23 H25 N5 O4; Mol wt: 435.4815

ACTION – Angiogenesis inhibitor for the treatment of cancer and rheumatoid arthritis and other disease states characterized by angiogenesis and increased vascular permeability that inhibits the effects of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) by interacting with VEGF and FGF R1 receptor tyrosine kinase, respectively. Compound also exhibited inhibition of growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC), and reduced the acute increase in uterine weight in rats following estrogen stimulation. Other particularly preferred compounds within this series of oxindolylquinazoline derivatives include the following:



Compound	R1	R2	R3	A	B	D	Formula
274814	H	1-imidazolidinyl	H	N	CH	CH	C ₂₁ H ₂₂ N ₆ O ₂
274816	H	4-morpholinyl	Me	N	N	CH	C ₂₂ H ₂₄ N ₆ O ₃
274818	OMe	4-morpholinyl	CF ₃	CH	CH	N	C ₂₄ H ₂₄ F ₃ N ₆ O ₄

SOURCE – Zeneca (AstraZeneca).

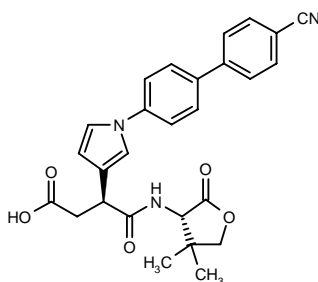
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1. Hennequin, L.F.A. et al. (Zeneca Ltd.) *Oxindolylquinazoline derivs.as angiogenesis inhibitors*. WO 9910349.

AG-3433*

264873

3(S)-[1-(4'-Cyanobiphenyl-4-yl)pyrrol-3-yl]-N-[4,4-dimethyl-2-oxotetrahydrofuran-3(S)-yl]succinamic acid



C27 H25 N3 O5; Mol wt: 471.5105

ACTION – Matrix metalloproteinase (MMP) inhibitor with potent activity against gelatinase A (MMP-2; K_i = 0.9 nM), collagenase 3 (MMP-13; K_i = 3.3 nM) and stromelysin 1 (MMP-3; K_i = 19 nM), but not against collagenase 1 (MMP-1; K_i = 14,188 nM) or matrilysin (MMP-7; K_i = 4545 nM), showing over 15,000-fold selectivity for MMP-2 over MMP-1. *In vivo*, compound (50-200 mg/kg p.o. b.i.d.) significantly decreased the growth of human colon and lung tumors implanted into nude mice and reduced the development of B16-F10 lesions in the lung of mice after i.v. implantation of tumor cells. Compound showed good oral and i.p. pharmacokinetic profiles, with an oral bioavailability of 21 and 82% in fed and fasted rats, respectively. A candidate for clinical development as a treatment for diseases related to MMP overexpression and activation, especially tumor growth and metastasis.

SOURCES – Agouron; Roche Bioscience.

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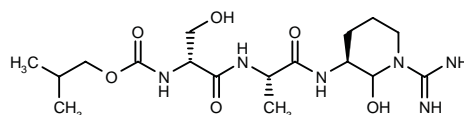
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3. Deal, J.G. et al. *Preparation of various P1'-heterocyclic succinamide inhibitors of matrix metalloproteases (MMP's)*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 197.
4. Koudriakova, T.B. et al. *AG3433 is a new orally available and metabolically stable MMP inhibitor*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3430.
5. Shalinsky, D.R. et al. *Development of a novel, highly-selective, potent MMP inhibitor, AG3433, with high oral bioavailability and antitumor activity*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3433.
6. Agouron R&D products will round out Warner-Lambert's pipeline. DailyDrugNews.com (Daily Essentials) 1999, Jan 29.

*Identified compound **264873** Drug Data Report 1998, 020(08): 0720.

CVS-2589

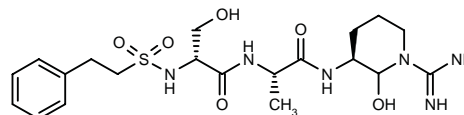
274067

N-(2-Methylpropxyphenyl)-D-seryl-L-alanine N-[1-carbamimidoyl-2-hydroxypiperidin-3(S)-yl]amide



C17 H32 N6 O6; Mol wt: 416.4758

ACTION – Potent inhibitor of urokinase plasminogen activator (uPA; K_i = 18.1 nM) with high selectivity versus other serine proteases including tissue plasminogen activator (tPA; K_i = 15 μM). Compound was orally bioavailable in dogs. Potentially useful for the prophylaxis and treatment of solid tumor metastasis and primary tumor growth, as well as for the treatment of excessive angiogenesis in diabetic retinopathy. Another peptidomimetic inhibitor of uPA is:



CVS-3083 [274071]: C20 H32 N6 O6 S

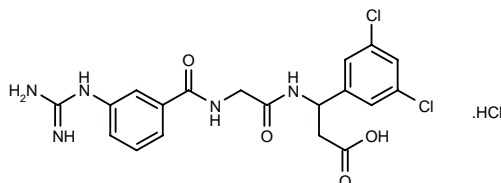
SOURCE – Corvas.

REFERENCES

1. Weinhouse, M.I. et al. *Synthesis and biological activity of transition-state urokinase inhibitors*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 090.

SC-68448**273795**

N-[2-[3-(Guanidino)benzamido]acetyl]-3-(3,5-dichlorophenyl)-β-alanine hydrochloride



C19 H19 Cl2 N5 O4 . HCl; Mol wt: 488.7570

ACTION – Angiogenesis inhibitor, a potent, selective and orally bioavailable antagonist of vitronectin binding to $\alpha_v\beta_3$ receptors (IC_{50} = 1.13 nM) with at least 100-fold selectivity over gpIIb/IIIa receptors. Compound exhibited anti-angiogenic activity *in vitro* and *in vivo*, as demonstrated by inhibition of both endothelial cell proliferation (IC_{50} = 1-10 μ M) and corneal neovascularization in rats (56% inhibition at 50 mg/kg i.p. b.i.d. for 7 days). In the SCID mouse Leydig cell tumor model, compound (50 mg/kg i.p. b.i.d. for 10 days) inhibited tumor growth by up to 80% and completely blocked the development of hypercalcemia related to tumor growth. When administered in combination with cisplatin, it showed good efficacy in reducing tumor volume.

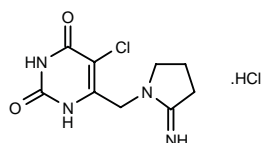
SOURCE – Searle.

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3. Ruminski, P.G. et al. *Potent, selective peptidomimetic antagonists of the $\alpha v\beta_3$ integrin and their *in vivo* efficacy in models of osteoporosis and cancer*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 144.

OTHER ONCOLYTIC DRUGS**268483**

5-Chloro-6-(2-iminopyrrolidin-1-ylmethyl)pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride



C9 H11 Cl N4 O2 . HCl; Mol wt: 279.1258

ACTION – Antineoplastic agent, a thymidine phosphorylase (TP; identical to platelet-derived endothelial cell growth factor) inhibitor proven to completely suppress angiogenesis by KB cells transfected with platelet-derived endothelial cell growth factor (KB/TP). In athymic nude mice, compound at an oral dose of 50 mg/kg/day significantly inhibited the growth of KB/TP xenografts and increased the apoptotic index in tumors.

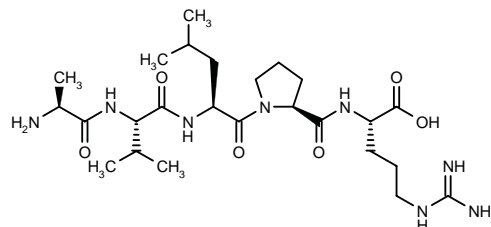
SOURCE – Taiho.

REFERENCES

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3. Matsushita, S. et al. *The effect of a thymidine phosphorylase inhibitor on angiogenesis and apoptosis in tumors*. Cancer Res 1999, 59(8): 1911.
4. Matsushita, S. et al. *The effect of a thymidine phosphorylase inhibitor on angiogenesis and apoptosis tumors*. Proc Amer Assoc Cancer Res 1999, 40: Abst 447.

273672

Alanyl-valyl-leucyl-prolyl-arginine



C25 H46 N8 O6; Mol wt: 554.6884

ACTION – Apoptosis-inducing peptide with potent activity against human erythroblast leukemia K562 cells.

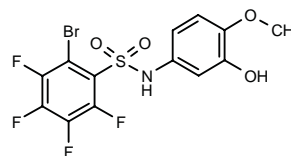
SOURCE – Morinaga Milk.

REFERENCES

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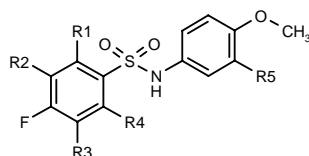
274269

2-Bromo-3,4,5,6-tetrafluoro-*N*-(3-hydroxy-4-methoxyphenyl)benzenesulfonamide



C13 H8 Br F4 N O4 S; Mol wt: 430.1712

ACTION – Antiproliferative and cholesterol-lowering agent with potent cytotoxic activity against HeLa cells *in vitro* (IC_{50} = 0.05 μ M) and also proven to increase LDL receptor expression in HepG2 cells, the minimum concentration capable of inducing maximal expression of LDL receptors being 0.15 μ M. Claimed for use in the treatment of cancer, microbial infections, psoriasis, vascular restenosis and hypercholesterolemia. Within this series of substituted benzene derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
274270	H	H	NO2	H	OH	C ₁₃ H ₁₁ FN ₂ O ₆ S
274271	F	F	F	Br	H	C ₁₃ H ₈ BrF ₄ NO ₃ S
274272	F	F	Br	F	H	C ₁₃ H ₈ BrF ₄ NO ₃ S
274273	F	Cl	Cl	F	H	C ₁₃ H ₆ Cl ₂ F ₃ NO ₃ S
274274	F	Cl	Cl	F	OH	C ₁₃ H ₆ Cl ₂ F ₃ NO ₄ S
274275	H	F	F	F	OH	C ₁₃ H ₉ F ₄ NO ₄ S

SOURCE – Tularik.

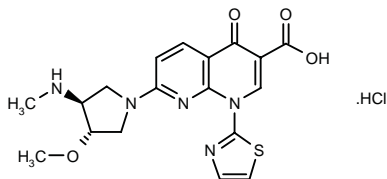
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AG-7352.HCl*

237721

(+)-7-[3(S)-Methoxy-4(S)-(methylamino)pyrrolidin-1-yl]-4-oxo-1-(2-thiazolyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrochloride



C₁₈ H₁₉ N₅ O₄ S . HCl; Mol wt: 437.9080

ACTION – Antineoplastic agent, a quinolone-related structure with broad-spectrum antitumor activity against a variety of human tumor cell lines including leukemia, ovarian, lung, stomach, colon, uterus, breast, bladder, pancreas and nasopharyngeal cancer cells (IC₅₀ = 0.0158-0.463 µg/ml). Compound displayed potent antitumor activity *in vivo* in mice bearing P388 leukemia, increasing survival by more than 275% at a dose of 12.5 mg/kg i.p. on days 1 and 5. Potent activity was also observed in the murine colon 26 tumor model (99% inhibition of tumor growth at 20 mg/kg i.v. every 7 days x 3; 2 of 6 mice cured) and the human ovarian cancer SK-OV-3 xenograft model (84% inhibition of tumor growth at 25 mg/kg i.v. every 7 days x 5). Compound has been selected for further evaluation.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

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*Identified compound **237721** (see **231743**) Drug Data Report 1996, 018(07): 0653.

ARSENIC TRIOXIDE

273556



As₂ O₃; Mol wt: 197.8410

ACTION – Antineoplastic agent with high clinical efficacy in patients with refractory or relapsed acute promyelocytic leukemia (APL). In a pilot study, 12 patients with APL who relapsed on or were refractory to conventional chemotherapy and *all-trans*-retinoic acid treated with the compound at doses of 0.06-0.2 mg/kg for 12-39 days i.v. showed complete remission. In another clinical study in 25 patients with relapsed APL, compound (10 mg i.v. for 28-56 days) induced complete remission in 96% of the treated patients, with no adverse events observed. The clinical response was associated with induction of apoptosis, caspase activation and incomplete cytodifferentiation in leukemic cells.

SOURCE – Shanghai Second Medical University, Shanghai (CN).

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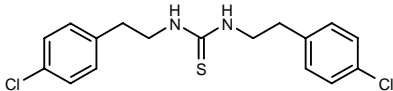
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DDE-380

273750

N,N'-Bis[2-(4-chlorophenyl)ethyl]thiourea



C17 H18 Cl2 N2 S; Mol wt: 353.3152

ACTION – Apoptosis-inducing agent from a series of thioureas.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

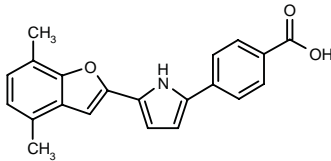
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ER-38925

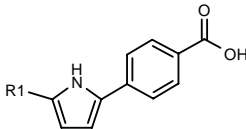
260592

4-[5-(4,7-Dimethylbenzofuran-2-yl)-1H-pyrrol-2-yl]benzoic acid



C21 H17 N O3; Mol wt: 331.3693

ACTION – High-affinity retinoic acid receptor- α (RAR α) agonist, potentially useful for the treatment of cancer, dermatological diseases and immunological disorders. Within this series of compounds characterized by a 2,5-disubstituted pyrrole moiety, the following are also included:



Compound	R1	Formula
ER-65250 [256149]	4-Me-7-Et-2-benzofuryl	C ₂₂ H ₁₉ NO ₃
ER-35368 [273761]	5,8-(Me)2-2-Naph	C ₂₃ H ₁₉ NO ₂
273762	4-CF3-7-F-2-benzofuryl	C ₂₀ H ₁₁ F ₄ NO ₃

SOURCE – Eisai.

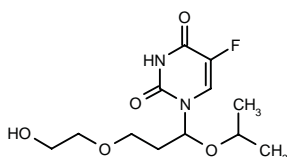
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GR-891

274985

5-Fluoro-1-[3-(2-hydroxyethoxy)-1-(isopropoxy)propyl]-pyrimidine-2,4(1*H*,3*H*)-dione



C12 H19 F N2 O5; Mol wt: 290.2891

ACTION – A 5-fluorouracil acyclonucleoside prodrug for differentiation therapy. Compound (22.5 and 45 μ M for 6 days) inhibited rhabdomyosarcoma RD cell growth without cytotoxicity and produced morphological and ultrastructural changes typical of myogenic transformation, associated with an increase in fibronectin but not P-glycoprotein expression.

SOURCE – Universidad de Granada, Granada (ES).

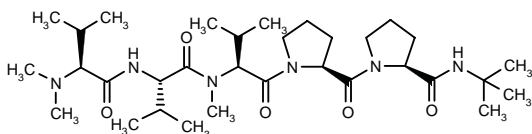
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LU-223651*

253902

N,N-Dimethyl-L-valyl-L-valyl-L-(*N*-methyl)valyl-L-prolyl-L-proline *tert*-butylamide



C32 H58 N6 O5; Mol wt: 606.8560

ACTION – Antineoplastic agent, an orally available analogue of cemadotin with *in vitro* cytotoxic activity against human colon carcinoma HT-29 cells (IC₅₀ = 80 nM) and tubulin polymerization-inhibitory activity (IC₅₀ = 10-20 μ M). Compared to cemadotin, title compound showed reduced *in vitro* potency but improved *in vivo* efficacy. Compound (every 2 days x 3 by i.v. injection

beginning on day 6, 13 or 20 after tumor transplantation) was curative in the human breast tumor MX-1 and LOX xenograft models in nude mice, even when treatment started at a late stage, and it induced significant tumor growth delay in human prostate PC-3, human lung LX-1 and human colon CX-1 xenografts. Compound also exhibited good antitumor activity after oral administration; preliminary pharmacokinetic studies showed an oral bioavailability of 50-80%. Currently undergoing phase I clinical studies.

SOURCE – BASF.

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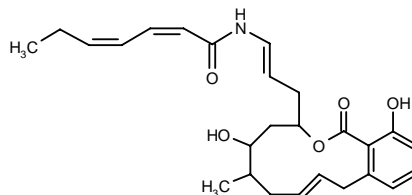
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*Identified compound **253902** (see **253496**) Drug Data Report 1997, 019(10): 0945.

SALICYLIHALAMIDE A

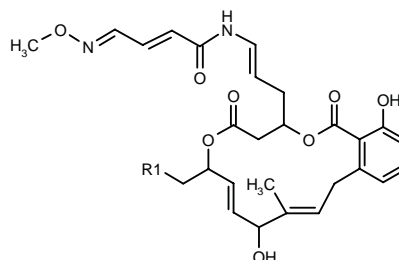
273004

N-[3-(5,14-Dihydroxy-6-methyl-1-oxo-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-3-yl)-1(*E*)-propenyl]-2(*Z*),4(*Z*)-heptadienamide

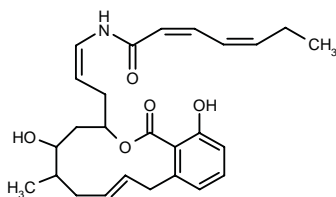


C26 H33 N O5; Mol wt: 439.5487

ACTION – Antineoplastic agent for the treatment of solid tumors, particularly tumors of the lung, brain, kidney and breast, as well as leukemia and melanoma, isolated from an extract of the marine sponge *Haliclona* sp. or the marine tunicate *Aplidium* sp. Compound exhibited high overall potency against the NCI 60 human tumor cell line panel (mean GI₅₀ about 15 nM). Other specifically claimed macrocyclic lactones isolated from these species include the following:



Compound	R1	Formula
Lobatamide C [273006]	H	C ₂₇ H ₃₂ N ₂ O ₈
Lobatamide F [273007]	OH	C ₂₇ H ₃₂ N ₂ O ₉



Salicylihalamide B [273005]: C₂₆ H₃₃ N O₅

SOURCE – Department of Health & Human Services (US).

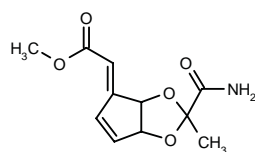
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SgnB

274029

2-[2-Carbamoyl-2-methyl-3a,6a-dihydro-4H-cyclopenta-[d][1,3]dioxol-4-ylidene]acetic acid methyl ester



C₁₁ H₁₃ N O₅; Mol wt: 239.2257

ACTION – Selective inhibitor of heat shock protein (HSP) gene expression produced by *Streptomyces* sp. AS9, potentially useful for reversing thermoresistance during heat therapy of cancer.

SOURCE – Mercian.

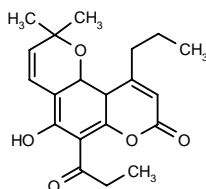
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WHI-D11

274043

5-Hydroxy-2,2-dimethyl-6-propanoyl-10-propyl-10a,10b-dihydro-2H,8H-pyrano[2,3-f][1]benzopyran-8-one



C₂₀ H₂₄ O₅; Mol wt: 344.4046

ACTION – Antineoplastic agent, a coumarin derivative that inhibits Bruton's tyrosine kinase (BTK; IC₅₀ = 29 μM) via binding to the catalytic site of the enzyme. Compound induced apoptotic cell death in human leukemia cells.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

REFERENCES

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CANCER GENE THERAPY

AS5-2H

274769

20-mer mixed-backbone oligonucleotide with the following sequence: 5'-UGACACCTGTTCTCACUCAC-3'; all internucleotide linkages are phosphorothioates and the first two and the last four nucleotides are 2'-MeO substituted

ACTION – Antisense oligonucleotide complementary to a portion of the RNA encoding MDM2, a protein overexpressed in a variety of tumors and shown to inhibit tumor suppressors such as p53, with potential for activating the expression of tumor suppressor genes for use in the treatment of cancer. Compound was shown to activate p53 expression *in vitro* in a variety of tumor cell lines. In addition, it was shown to produce growth arrest and apoptosis in several tumor cell lines at 200 nM. When tested *in vivo* in nude mice bearing osteosarcoma SJSA xenografts, it was shown to dose-dependently inhibit tumor growth following i.p. administration; a clear synergistic effect was observed when compound (5 mg/kg/day i.p.) was combined with 10-hydroxycamptothecin (3 mg/kg/day i.p.), the tumor growth being 11.2% relative to controls compared to values of 79.8 and 63.2% for compound and 10-hydroxycamptothecin alone, respectively, when given at the same dose levels used in the combination.

SOURCE – Hybridon.

REFERENCES

1. Chen, J. et al. (Hybridon, Inc.) *MDM2-specific antisense oligonucleotides*. WO 9910486.

ISIS-12539

274087

20-mer phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-CTCTCTGTAGGCCCGCTTGG-3'

ACTION – Antisense oligonucleotide for modulating the expression of Jun N-terminal kinases (JNK), which are involved in the activation of the transcription factor AP-1, which in turn has been implicated in abnormal cell proliferation and tumor formation, development and maintenance. Compound produced 91% inhibition of JNK1 mRNA expression in human lung carcinoma A-549 cells at a concentration of 400 nM. Potentially useful in the treatment of cancer and other hyperproliferative disorders.

SOURCE – Isis Pharmaceuticals.

REFERENCES

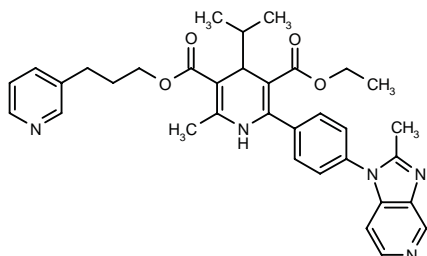
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

N276-15*

266982

4-Isopropyl-2-methyl-6-[4-(2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylic acid 5-ethyl 3-[3-(3-pyridyl)propyl] diester



C34 H37 N5 O4; Mol wt: 579.6973

ACTION – Dihydropyridine derivative with the ability to overcome multidrug resistance (MDR), as demonstrated in cultured KB/JV300 human cancer cells and in leukemia-bearing animals. At a dose of 20 mg/kg i.v., compound significantly increased life span in mice bearing leukemia P388 when administered in combination with etoposide. It shows markedly reduced undesirable effects such as calcium-antagonist activity.

SOURCE – Nikken Chemicals.

REFERENCES

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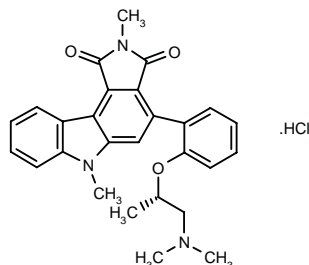
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*Identified compound **266982** (see **266185**) Drug Data Report 1998, 020(11): 0996.

CHEMOPROTECTIVE AGENTS

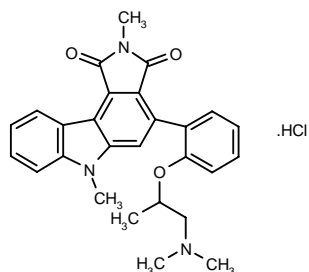
274058

4-[2-[2-(Dimethylamino)-1(*S*)-methylethoxy]phenyl]-6-methylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione hydrochloride



C27 H27 N3 O3 . HCl; Mol wt: 477.9892

ACTION – Pyrrolocarbazole derivative, the (*S*)-enantiomer of **KF-27376**, with thrombopoietic activity, proven to increase the number of megakaryocyte colonies (130% at 1 nM) and to enhance NF-E2 (p45) expression in hematopoietic cells. *In vivo*, compound reduced thrombocytopenia in both mitomycin C- and X-irradiation-treated mice (25 mg/kg b.i.d. x 10 p.o. and 10 mg/kg x 5 s.c., respectively).



KF-27376 [274060]: C27 H27 N3 O3 . HCl

SOURCE – Kyowa Hakko.

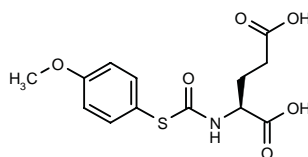
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274725

N-(4-Methoxyphenylsulfanylcarbonyl)-L-glutamic acid



C13 H15 N O6 S; Mol wt: 313.3285

M.p. 115 °C.

ACTION – Noncompetitive carboxypeptidase G₂ (CPG₂) inhibitor ($K_i = 0.3 \mu\text{M}$) useful in the antibody-directed enzyme prodrug therapy (ADEPT) of cancer for increasing the differential concentration of active enzyme between the tumor site and normal host tissues, resulting in minimal host tissue toxicity when the prodrug is administered early after the antibody–enzyme conjugate.

SOURCES – Enzacta; Imperial College of Science, Technology and Medicine, London (GB); University of Reading, Reading (GB).

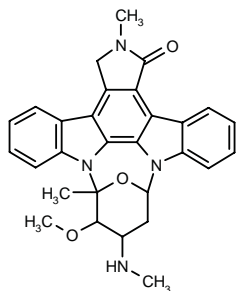
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2. Khan, T.H. et al. *Novel inhibitors of carboxypeptidase G₂ (CPG₂): Potential use in antibody-directed enzyme prodrug therapy*. *J Med Chem* 1999, 42(6): 951.

KT-6352*

219201

9,13-Epoxy-10-methoxy-2,9-dimethyl-11-(methylamino)-2,3,10,11,12,13-hexahydro-1*H*,9*H*-diindolo-[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-1-one



C29 H28 N4 O3; Mol wt: 480.5720

ACTION – Staurosporine derivative with thrombopoietic activity. *In vitro*, it stimulated bone marrow cells to increase the number of megakaryocyte (Meg) colonies in the presence of recombinant murine IL-3 (25-68% increase at 0.1-1 nM). *In vivo* in mice, compound (10 mg/kg/day x 5 days) induced a rapid and significant increase in peripheral platelet count, detectable from 9-27 days after the start of treatment, with a peak response on day 14. A marked increase in the number of colony-forming units (CFU) of Meg in bone marrow and spleen was observed, together with an increase in Meg ploidy. Potentially useful for the treatment of thrombocytopenia associated with radiotherapy and chemotherapy.

SOURCE – Kyowa Hakko.

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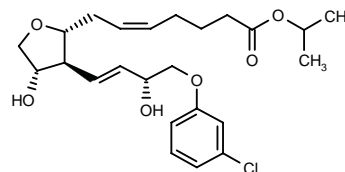
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4. Shiotsu, Y. et al. *In vitro and in vivo effects of KT6352, a derivative of indolocarbazole compounds, on murine megakaryocytopoiesis*. *Exp Hematol* 1998, 26(13): 1195.

*Identified compound **219201** (see **214886**) Drug Data Report 1995, 017(04): 0387.

OCULAR MEDICATIONS

274592

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9-oxa-prostaglandin E₂ isopropyl ester



C24 H33 Cl O6; Mol wt: 452.9717

ACTION – Agent for the treatment of glaucoma and ocular hypertension, a prostaglandin analogue reported to possess functional prostaglandin DP and/or FP receptor agonist-activity and reduced side effects.

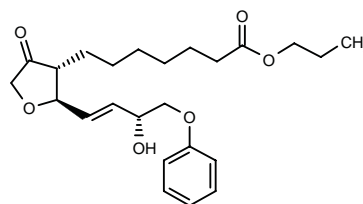
SOURCE – Alcon.

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1. Selliah, R.D. (Alcon Laboratories, Inc.) *9-Oxa prostaglandin analogs as ocular hypotensives*. WO 9857942.

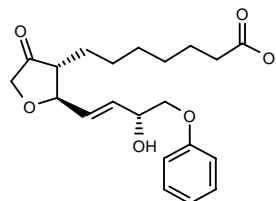
274641

16-Phenoxy-17,18,19,20-tetranor-11-oxaprostaglandin E₁ propyl ester



C24 H34 O6; Mol wt: 418.5266

ACTION – Prostaglandin E (PGE) analogue with potential in the treatment of glaucoma and ocular hypertension, reported to possess functional EP receptor-agonist activity. Another specifically claimed compound from this series of keto-substituted tetrahydrofuran analogues of prostaglandins is:



274642: C21 H28 O6

ACTION – Noncompetitive carboxypeptidase G₂ (CPG₂) inhibitor ($K_i = 0.3 \mu\text{M}$) useful in the antibody-directed enzyme prodrug therapy (ADEPT) of cancer for increasing the differential concentration of active enzyme between the tumor site and normal host tissues, resulting in minimal host tissue toxicity when the prodrug is administered early after the antibody–enzyme conjugate.

SOURCES – Enzacta; Imperial College of Science, Technology and Medicine, London (GB); University of Reading, Reading (GB).

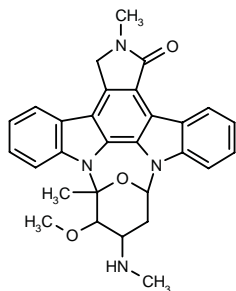
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1. Khan, T. (Aepact Ltd.) *Drug therapy*. WO 9720580.
2. Khan, T.H. et al. *Novel inhibitors of carboxypeptidase G₂ (CPG₂): Potential use in antibody-directed enzyme prodrug therapy*. J Med Chem 1999, 42(6): 951.

KT-6352*

219201

9,13-Epoxy-10-methoxy-2,9-dimethyl-11-(methylamino)-2,3,10,11,12,13-hexahydro-1*H*,9*H*-diindolo-[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-1-one



C29 H28 N4 O3; Mol wt: 480.5720

ACTION – Staurosporine derivative with thrombopoietic activity. *In vitro*, it stimulated bone marrow cells to increase the number of megakaryocyte (Meg) colonies in the presence of recombinant murine IL-3 (25-68% increase at 0.1-1 nM). *In vivo* in mice, compound (10 mg/kg/day x 5 days) induced a rapid and significant increase in peripheral platelet count, detectable from 9-27 days after the start of treatment, with a peak response on day 14. A marked increase in the number of colony-forming units (CFU) of Meg in bone marrow and spleen was observed, together with an increase in Meg ploidy. Potentially useful for the treatment of thrombocytopenia associated with radiotherapy and chemotherapy.

SOURCE – Kyowa Hakko.

REFERENCES

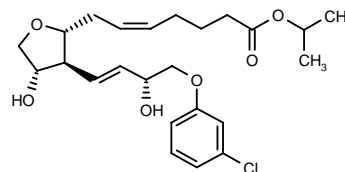
1. Murakata, C. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Indolocarbazole derivs. and their use in the treatment of thrombocytopenia*. EP 672668, JP 96283271, US 5604219.
2. Murakata, C. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Sensitivity enhancer for antineoplastic agent*. EP 643966, JP 95519798, WO 9420106.
3. Ikuina, Y. et al. *Synthesis and structure-activity relationships of pyrrolocarbazole derivatives possessing thrombopoietic activity*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 089.
4. Shiotsu, Y. et al. *In vitro and in vivo effects of KT6352, a derivative of indolocarbazole compounds, on murine megakaryocytopoiesis*. Exp Hematol 1998, 26(13): 1195.

*Identified compound **219201** (see **214886**) Drug Data Report 1995, 017(04): 0387.

OCULAR MEDICATIONS

274592

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9-oxa-prostaglandin E₂ isopropyl ester



C24 H33 Cl O6; Mol wt: 452.9717

ACTION – Agent for the treatment of glaucoma and ocular hypertension, a prostaglandin analogue reported to possess functional prostaglandin DP and/or FP receptor agonist-activity and reduced side effects.

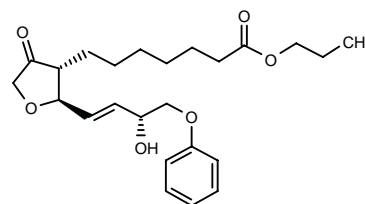
SOURCE – Alcon.

REFERENCES

1. Selliah, R.D. (Alcon Laboratories, Inc.) *9-Oxa prostaglandin analogs as ocular hypotensives*. WO 9857942.

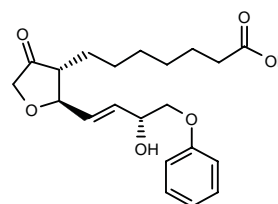
274641

16-Phenoxy-17,18,19,20-tetranor-11-oxaprostaglandin E₁ propyl ester



C24 H34 O6; Mol wt: 418.5266

ACTION – Prostaglandin E (PGE) analogue with potential in the treatment of glaucoma and ocular hypertension, reported to possess functional EP receptor-agonist activity. Another specifically claimed compound from this series of keto-substituted tetrahydrofuran analogues of prostaglandins is:



274642: C21 H28 O6

SOURCE – Alcon.

REFERENCES

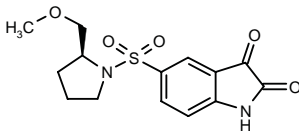
1. Selliah, R.D. (Alcon Laboratories, Inc.) *Keto-substd. tetrahydrofuran analogs of prostaglandins as ocular hypotensives*. US 5866602, WO 9857930.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

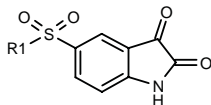
273300

(+)-5-[2(S)-(Methoxymethyl)pyrrolidin-1-ylsulfonyl]-indoline-2,3-dione



C14 H16 N2 O5 S; Mol wt: 324.3554

ACTION – An inhibitor of caspases, particularly caspases 3 and 7, with potential in the treatment of diseases caused by excessive or inappropriate apoptosis such as Alzheimer’s disease, viral infections, infarction, reperfusion injury, ischemia, bone loss, osteoarthritis and hepatocellular degeneration. Compound blocks the production of IL-1β and/or tumor necrosis factor (TNF). Other specifically claimed compounds within this series of indoline-2,3-dione derivatives include the following:



Compound	R1	Formula
273301	N(Me)CH2CH2OH	C ₁₁ H ₁₂ N ₂ O ₅ S
273302	2(S)-(CO2Me)-1-pyrrolidinyl	C ₁₄ H ₁₄ N ₂ O ₆ S
273303	2(S)-(PhNHCH2)-1-pyrrolidinyl	C ₁₉ H ₁₉ N ₃ O ₄ S
273304	2(S)-(PhSCH2)-1-pyrrolidinyl	C ₁₉ H ₁₈ N ₂ O ₄ S ₂
273305	2(S)-[3,4-(Cl)2-PhOCH2]-1-pyrrolidinyl	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₅ S

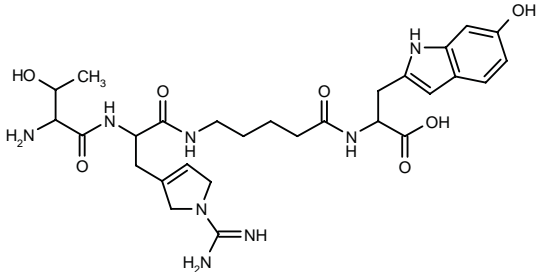
SOURCE – SmithKline Beecham.

REFERENCES

1. Lee, D. and Long, S.A. (SmithKline Beecham Corp.) *Caspases and apoptosis*. WO 9906367.

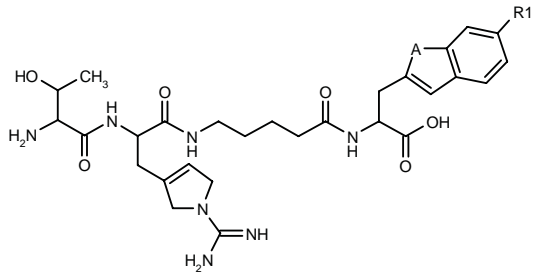
274386

2-[5-[3-(1-Amidino-2,5-dihydropyrrol-3-yl)-2-(D,L-threonyl-amino)propionamido]pentanamido]-3-(6-hydroxy-1H-indol-2-yl)propionic acid



C28 H40 N8 O7; Mol wt: 600.6730

ACTION – Agent for the treatment or prevention of bone disorders such as osteoporosis, as well as rheumatoid arthritis, osteoarthritis and degenerative arthrosis, that acts by stimulating bone formation, as demonstrated *in vitro* in fetal rat calvaria cultures at 0.001-10 µg/ml. Other exemplified compounds from this series of peptides containing an arginine mimetic include the following:



Compound	R1	A	Formula
274387	H	S	C ₂₈ H ₃₉ N ₇ O ₆ S
274388	Me	NH	C ₂₉ H ₄₂ N ₈ O ₆

SOURCE – Roche Diagnostics.

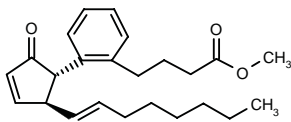
REFERENCES

1. Esswein, A. et al. (Roche Diagnostics GmbH) *Peptide containing an arginine mimetic for the treatment of osteoporosis, their production, and drugs containing these cpds..* EP 902036, WO 9912970.

274563

4-[2-[(1R*,2R*)-2-[1(E)-Octenyl]-5-oxo-3-cyclopenten-1-yl]phenyl]butyric acid methyl ester

DL-15-Deoxy-5,6,7-trinor-4,8-inter-o-phenyleneprostaglandin A₁ methyl ester



C24 H32 O3; Mol wt: 368.5138

ACTION – Prostaglandin A₁ analogue shown to stimulate bone formation in cultured human osteoblasts at 50 nM.

SOURCE – Alcon.

REFERENCES

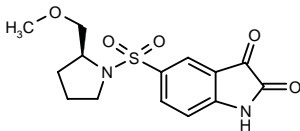
1. Selliah, R.D. (Alcon Laboratories, Inc.) *Keto-substd. tetrahydrofuran analogs of prostaglandins as ocular hypotensives*. US 5866602, WO 9857930.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

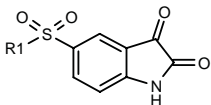
273300

(+)-5-[2(S)-(Methoxymethyl)pyrrolidin-1-ylsulfonyl]-indoline-2,3-dione



C14 H16 N2 O5 S; Mol wt: 324.3554

ACTION – An inhibitor of caspases, particularly caspases 3 and 7, with potential in the treatment of diseases caused by excessive or inappropriate apoptosis such as Alzheimer’s disease, viral infections, infarction, reperfusion injury, ischemia, bone loss, osteoarthritis and hepatocellular degeneration. Compound blocks the production of IL-1β and/or tumor necrosis factor (TNF). Other specifically claimed compounds within this series of indoline-2,3-dione derivatives include the following:



Compound	R1	Formula
273301	N(Me)CH2CH2OH	C11H12N2O5S
273302	2(S)-(CO2Me)-1-pyrrolidinyl	C14H14N2O6S
273303	2(S)-(PhNHCH2)-1-pyrrolidinyl	C19H19N3O4S
273304	2(S)-(PhSCH2)-1-pyrrolidinyl	C19H18N2O4S2
273305	2(S)-[3,4-(Cl)2-PhOCH2]-1-pyrrolidinyl	C19H16Cl2N2O5S

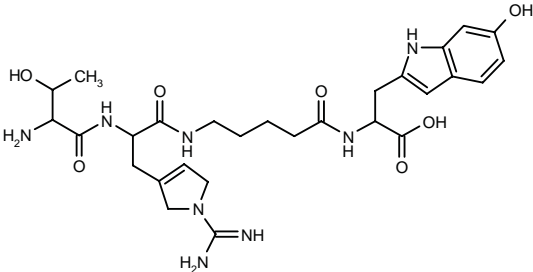
SOURCE – SmithKline Beecham.

REFERENCES

1. Lee, D. and Long, S.A. (SmithKline Beecham Corp.) *Caspases and apoptosis*. WO 9906367.

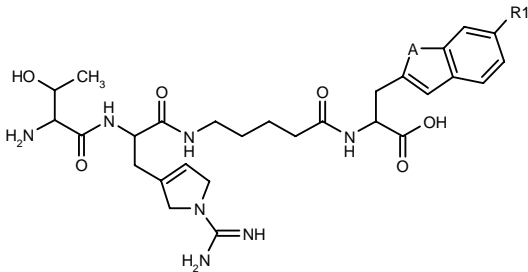
274386

2-[5-[3-(1-Amidino-2,5-dihydropyrrol-3-yl)-2-(D,L-threonyl-amino)propionamido]pentanamido]-3-(6-hydroxy-1H-indol-2-yl)propionic acid



C28 H40 N8 O7; Mol wt: 600.6730

ACTION – Agent for the treatment or prevention of bone disorders such as osteoporosis, as well as rheumatoid arthritis, osteoarthritis and degenerative arthrosis, that acts by stimulating bone formation, as demonstrated *in vitro* in fetal rat calvaria cultures at 0.001-10 µg/ml. Other exemplified compounds from this series of peptides containing an arginine mimetic include the following:



Compound	R1	A	Formula
274387	H	S	C28H39N7O6S
274388	Me	NH	C29H42N8O6

SOURCE – Roche Diagnostics.

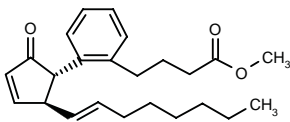
REFERENCES

1. Esswein, A. et al. (Roche Diagnostics GmbH) *Peptide containing an arginine mimetic for the treatment of osteoporosis, their production, and drugs containing these cpds..* EP 902036, WO 9912970.

274563

4-[2-[(1R*,2R*)-2-[1(E)-Octenyl]-5-oxo-3-cyclopenten-1-yl]phenyl]butyric acid methyl ester

DL-15-Deoxy-5,6,7-trinor-4,8-inter-o-phenyleneprostaglandin A1 methyl ester



C24 H32 O3; Mol wt: 368.5138

ACTION – Prostaglandin A1 analogue shown to stimulate bone formation in cultured human osteoblasts at 50 nM.

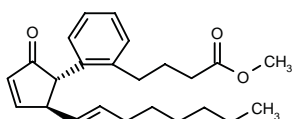
SOURCE – Taisho.

REFERENCES

1. Tanami, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Prostaglandin A₁ analogs*. JP 99043461.

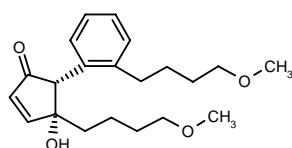
274603

4-[2-[(1*R**,2*R**)-2-Hydroxy-2-(4-methoxybutyl)-5-oxo-3-cyclopenten-1-yl]phenyl]butyric acid methyl ester



C21 H28 O5; Mol wt: 360.4472

ACTION – Agent for the treatment of osteoporosis with potent bone formation-promoting effects, as demonstrated *in vitro* by the ability to increase calcium content and alkaline phosphatase activity in human osteoblasts (1758 and 271%, respectively, at 5 μ M). Another compound from this series of hydroxycyclopentenone derivatives is:



274604: C21 H30 O4

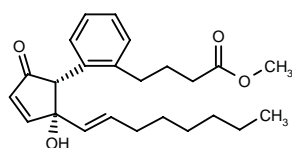
SOURCE – Taisho.

REFERENCES

1. Tanami, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Phenyl-substd. hydroxy cyclopentenone analogs*. JP 99043460.

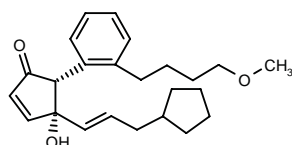
274605

4-[2-[(1*R**,2*R**)-2-Hydroxy-2-[1(*E*)-octenyl]-5-oxo-3-cyclopenten-1-yl]phenyl]butyric acid methyl ester



C24 H32 O4; Mol wt: 384.5128

ACTION – Agent for the treatment of osteoporosis with good bone formation-promoting effects, as demonstrated *in vitro* by the ability to increase calcium content and alkaline phosphatase activity in human osteoblasts (475 and 139%, respectively, at 5 μ M). Another compound from this series of hydroxycyclopentenone derivatives is:



274606: C24 H32 O3

SOURCE – Taisho.

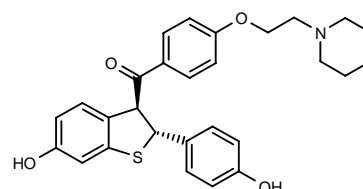
REFERENCES

1. Tanami, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Phenyl-substd. hydroxy cyclopentenone analogs*. JP 99043459.

DIHYDRORALOXIFENE

274048

trans-[6-Hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1-benzo[*b*]thiophen-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone



C28 H29 N O4 S; Mol wt: 475.6061

ACTION – Selective estrogen receptor modulator (SERM) with estrogen receptor binding affinity comparable to raloxifene, as measured by displacement of [³H]-17 β -estradiol binding in MCF-7 cell lysates. *In vitro*, compound exhibited potent estrogen-antagonist activity, as demonstrated by inhibition of 17 β -estradiol-stimulated proliferation of MCF-7 cells (IC₅₀ = 0.52 nM vs. 0.34 nM for raloxifene). Potentially useful for the treatment and/or prevention of osteoporosis, breast cancer, hypercholesterolemia, Alzheimer's disease and postmenopausal complications in women.

SOURCE – Lilly.

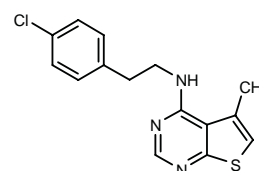
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1. Misner, J.W. and Schmid, C.R. (Eli Lilly and Company) *Intermediates and processes for preparing benzo[*b*]thiophenes*. WO 9848793.
2. Schmid, C.R. et al. *Synthesis and biological activity of dihydroralexifene*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 072.
3. Schmid, C.R. et al. *Synthesis and biological activity of trans-2,3-dihydroralexifene*. Bioorg Med Chem Lett 1999, 9(8): 1137.

NSL-1406

274853

N-[2-(4-Chlorophenyl)ethyl]-5-methylthieno[2,3-*d*]-pyrimidin-4-amine



C15 H14 Cl N3 S; Mol wt: 303.8156

ACTION – Cytotoxic agent active against several cell types of hematopoietic origin such as leukemia cells (IC_{50} = 5.2, 5.0 and 8.5 nM, respectively, at 24 h against P388, J774 and HL-60 cell lines) and osteoclasts, but not against nonhematopoietic adhesive cells; it also suppressed *in vitro* bone resorption at submicromolar concentrations (IC_{50} = 4 nM). The cytotoxic concentration of the compound was about 10,000-fold lower than its lethal concentration (LC_{50} = 35, 43 and 67 μ M for P388, J744 and HL-60 cell lines, respectively). It appears to act as an integrin $\alpha_v\beta_3$ (vitronectin receptor) antagonist (IC_{50} = 50 μ M), but this effect can not solely explain its cytotoxic activity. It may be particularly useful for the treatment of osteoporosis or inflammation.

SOURCE – Nippon Steel.

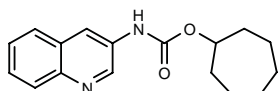
REFERENCES

1. Katada, J. et al. *Cytotoxic effects of NSL-1406, a new thienopyrimidine derivative, on leukocytes and osteoclasts*. *Bioorg Med Chem Lett* 1999, 9(6): 797.

TREATMENT OF LIPOPROTEIN DISORDERS

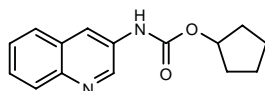
274550

N-(3-Quinoliny)carbamic acid cycloheptyl ester



C17 H20 N2 O2; Mol wt: 284.3570

ACTION – Hypolipidemic and hypocholesterolemic agent that acts by stimulating the expression of the LDL receptor gene, as demonstrated in transfected CHO cells by a 5-fold increase in LDL receptor gene expression at concentrations of 0.01-0.1 μ M. Another compound from this series of carbamate derivatives is:



274551: C15 H16 N2 O2

SOURCE – Tanabe.

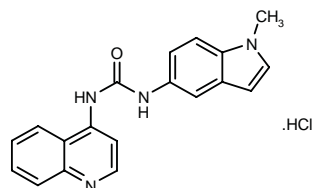
REFERENCES

1. Horikawa, K. et al. (Tanabe Seiyaku Co., Ltd.) *Urethane derivs*. JP 99035545.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

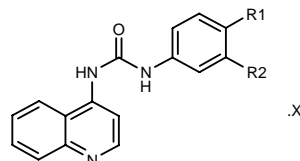
274025

N-(1-Methyl-1*H*-indol-5-yl)-*N'*-(4-quinolinyl)urea hydrochloride



C19 H16 N4 O . HCl; Mol wt: 352.8233

ACTION – Nonpeptide antagonist of human 7-transmembrane G-protein-coupled neuropeptide receptor HFGAN72 (pK_b > 7) with potential in the treatment or prevention of disorders mediated by this receptor such as obesity and sleep disorders. Other compounds from this series of phenyl urea and phenyl thiourea derivatives include the following:



Compound	R1	R2	X	Formula
274026	SMe	H	HCl	C ₁₇ H ₁₅ N ₃ OS.HCl
274027	N(Me) ₂	H	2HCl	C ₁₈ H ₁₈ N ₄ O.2HCl
274028	OMe	Cl	HCl	C ₁₇ H ₁₄ ClN ₃ O ₂ .HCl

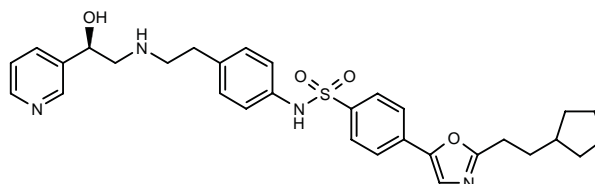
SOURCE – SmithKline Beecham.

REFERENCES

1. Chan, G. et al. (SmithKline Beecham plc) *Phenyl urea and phenyl thiourea derivs. as HFGAN72 antagonists*. WO 9909024.

274074

4-[2-(2-Cyclopentylethyl)-5-oxazolyl]-*N*-[4-[2-[2(*R*)-hydroxy-2-(3-pyridinyl)ethylamino]ethyl]phenyl]benzenesulfonamide



C31 H36 N4 O4 S; Mol wt: 560.7154

ACTION – Potent human β_3 -adrenoceptor agonist (EC_{50} = 18 nM for stimulation of cAMP in CHO cells expressing the cloned human receptor) with little binding affinity for β_1 - and β_2 -adrenoceptors (IC_{50} = 4800 and 1800 nM, respectively). Compound induced hyperglycerolemia in anesthetized monkeys (ED_{50} = 0.09 mg/kg i.v.). It had excellent oral bioavailability (38%) in dogs, with a half-life of 5 h, and significantly increased plasma glycerol levels when given orally (10 mg/kg); compound did not affect heart rate. Potentially useful for the treatment of metabolic syndromes such as obesity, diabetes and cardiovascular diseases.

SOURCE – Merck & Co.

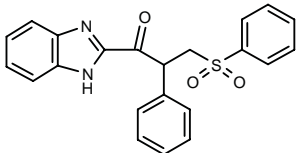
REFERENCES

1. Fisher, M.H. et al. (Merck & Co., Inc.) *Substd. sulfonamides as selective beta3 agonists for the treatment of diabetes and obesity*. EP 757674, JP 97512275, US 5541197, US 5561142, WO 9529159.

2. Ok, H.O. et al. *Substituted oxazole benzenesulfonamides as potent human beta3 adrenergic receptor agonists*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 114.

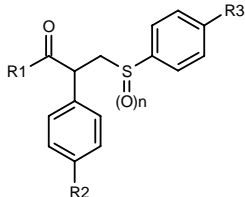
274493

1-(1*H*-Benzimidazol-2-yl)-2-phenyl-3-(phenylsulfonyl)-1-propanone



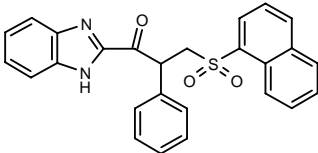
C22 H18 N2 O3 S; Mol wt: 390.4612

ACTION – Selective neuropeptide Y (NPY) Y_5 receptor antagonist, as demonstrated in binding assays by IC_{50} values of 0.011, 0.022, > 5, > 5 and > 5 μ M for rat Y_5 and human Y_5 , Y_1 , Y_2 and Y_4 receptors, respectively. Potentially useful in the treatment of obesity, bulimia nervosa, sexual dysfunction, reproductive disorders, depression, anxiety, gastric ulcers, memory loss, migraine, pain, epileptic seizures, hypertension, cerebral hemorrhage, shock, congestive heart failure, sleep disorders, nasal congestion and diarrhea. Within this series of heterocyclic ketones, the following compounds are also included:



Compound	R1	R2	R3	n	Formula
274494	2-quinolinyl	H	Me	2	C ₂₆ H ₂₁ NO ₃ S
274495	2-imidazolyl	H	Me	0	C ₁₉ H ₁₈ N ₂ OS
274508	2-imidazolyl	H	Me	2	C ₁₉ H ₁₈ N ₂ O ₃ S
274509	2-benzimidazolyl	H	Me	0	C ₂₃ H ₂₀ N ₂ OS
274510	2-benzimidazolyl	H	Me	1	C ₂₃ H ₂₀ N ₂ O ₂ S
274511	2-benzothiazolyl	H	Me	2	C ₂₃ H ₁₉ NO ₃ S ₂
274512	5,6-(Me)2-2-benzimidazolyl	H	Me	2	C ₂₈ H ₂₄ N ₂ O ₃ S

Compound	R1	R2	R3	n	Formula
274513	2-benzimidazolyl	F	Me	2	C ₂₃ H ₁₉ FN ₂ O ₃ S
274514	2-benzimidazolyl	H	OMe	2	C ₂₃ H ₂₀ N ₂ O ₄ S
274515	2-benzimidazolyl	H	Br	2	C ₂₂ H ₁₇ BrN ₂ O ₃ S
274517	5-Me-2-benzimidazolyl	H	Me	2	C ₂₄ H ₂₂ N ₂ O ₃ S
274518	5-MeO-2-benzimidazolyl	H	Me	2	C ₂₄ H ₂₂ N ₂ O ₄ S
274519	2-benzimidazolyl	H	Me	2	C ₂₃ H ₂₀ N ₂ O ₃ S



274516: C26 H20 N2 O3 S

SOURCE – Bayer.

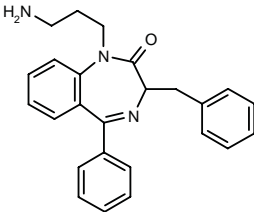
REFERENCES

1. Connell, R.D. et al. (Bayer Corp.) *Heterocyclic ketones as NPY Y₅ antagonists*. WO 9910330.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

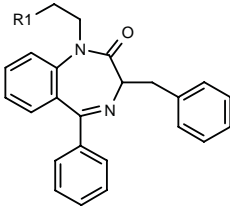
272831

(±)-1-(3-Aminopropyl)-3-benzyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one



C25 H25 N3 O; Mol wt: 383.4925

ACTION – Agent for regulating platelet production with affinity for the thrombopoietin (TPO) receptor. A representative compound from a series of 1,4-benzodiazepin-2-one derivatives, wherein the following are also included:



Compound	R1	Formula
272832	NH2	C ₂₆ H ₂₄ N ₄ O
272833	CH2NH2	C ₂₇ H ₂₆ N ₄ O
272834	CH2CH2NH2	C ₂₈ H ₂₈ N ₄ O

SOURCE – Hokuriku.

REFERENCES

1. Watanabe, Y. et al. (Hokuriku Seiyaku Co., Ltd.) *1,4-Benzodiazepine derivs. and their use*. JP 99001477.

DIAGNOSTIC AGENTS

273926

DNA fragment (5516-7091) derived from the genomic DNA of HPV-33

ACTION – Immunogenic peptide derived from genomic DNA of human papillomavirus type 33 (HPV-33), claimed for use in the detection of HPV in tissue cultures, and thus the possible development of invasive cervical carcinomas.

SOURCE – Institut Pasteur, Paris (FR).

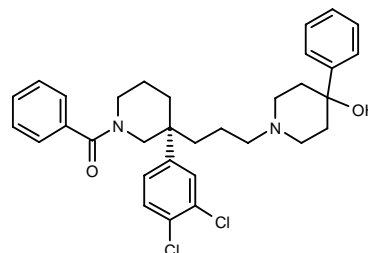
REFERENCES

1. Cole, S. and Streeck, R.E. (Institut Pasteur) *Purified human papillomavirus type 33 (HPV-33) peptides as an immunogenic compsn*. US 5876723.

PHARMACOLOGICAL TOOLS

274750

1-Benzoyl-3(*R*)-(3,4-dichlorophenyl)-3-[3-(4-hydroxy-4-phenylpiperidin-1-yl)propyl]piperidine



C32 H36 Cl2 N2 O2; Mol wt: 551.5544

ACTION – Nonpeptide tachykinin NK₃ antagonist (IC₅₀ = 5.9 nM) whose activity is at least 7-fold less potent than the reference NK₃ antagonist SR-142801, but which shows improved oral bioavailability and relatively slow clearance following administration of a dose of 20 mg/kg to rats (t_{1/2} = 6.4 and 1.9 h for compound and SR-142801, respectively; AUC = 2081 and 1080 µg/h/l, respectively).

SOURCE – Warner-Lambert.

REFERENCES

1. Chen, M.H.G. et al. (Warner-Lambert Co.) *3-Alkyl-3-phenyl-piperidines*. WO 9811090.
2. Chen, M.H. et al. *Syntheses and biological activities of chiral piperidines-tachykinin NK3 antagonists*. Acta Pharmacol Sin 1999, 20(3): 283.

SOURCE – Hokuriku.

REFERENCES

1. Watanabe, Y. et al. (Hokuriku Seiyaku Co., Ltd.) *1,4-Benzodiazepine derivs. and their use*. JP 99001477.

DIAGNOSTIC AGENTS

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SOURCE – Institut Pasteur, Paris (FR).

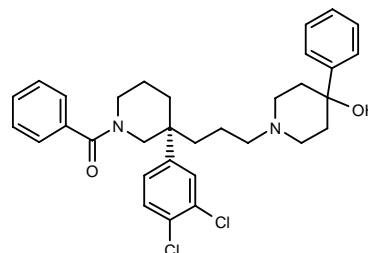
REFERENCES

1. Cole, S. and Streeck, R.E. (Institut Pasteur) *Purified human papillomavirus type 33 (HPV-33) peptides as an immunogenic compsn*. US 5876723.

PHARMACOLOGICAL TOOLS

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SOURCE – Warner-Lambert.

REFERENCES

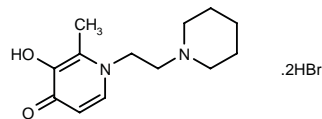
1. Chen, M.H.G. et al. (Warner-Lambert Co.) *3-Alkyl-3-phenyl-piperidines*. WO 9811090.
2. Chen, M.H. et al. *Syntheses and biological activities of chiral piperidines-tachykinin NK3 antagonists*. Acta Pharmacol Sin 1999, 20(3): 283.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

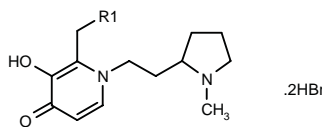
274957

3-Hydroxy-2-methyl-1-[2-(1-piperidiny)ethyl]pyridin-4(1H)-one dihydrobromide



C13 H20 N2 O2 . 2HBr; Mol wt: 398.1368

ACTION – Analgesic agent with significantly greater potency compared to acetylsalicylic acid in the mouse writhing test (81.7% vs. 50.70% at 100 mg/kg i.p.). Compound also showed significant antiinflammatory activity against carrageenan-induced paw edema in mice (53.3% inhibition of edema at 100 mg/kg i.p.), being more active than indomethacin. Other related 4(1H)-pyridinone derivatives include the following:



Compound	R1	Formula
274851	H	C ₁₃ H ₂₀ N ₂ O ₂ .2HBr
274852	Me	C ₁₄ H ₂₂ N ₂ O ₂ .2HBr

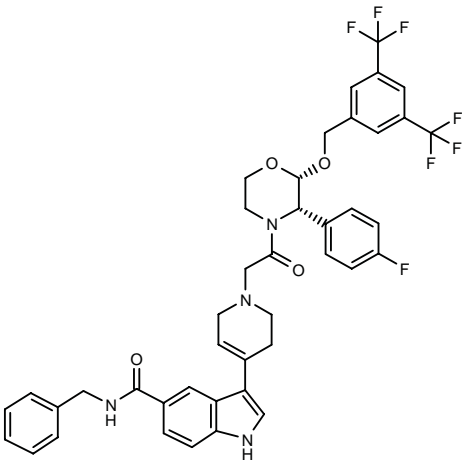
SOURCE – Hacettepe University, Ankara (TR).

REFERENCES

1. Aytemir, M.D. et al. *New 4(1H)-pyridinone derivatives as analgesic agents*. *Arzneim-Forsch Drug Res* 1999, 49(3): 250.

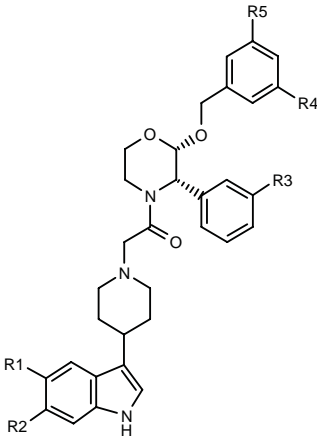
275373

3-[1-[2-[(2S,3S)-2-[3,5-Bis(trifluoromethyl)benzyloxy]-3-(4-fluorophenyl)-4-morpholinyl]-2-oxoethyl]-1,2,3,6-tetrahydro-4-pyridinyl]-N-benzyl-1H-indole-5-carboxamide

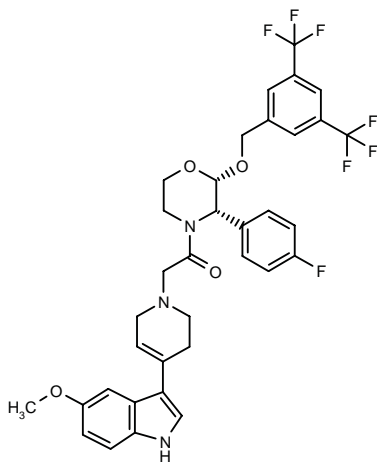


C42 H37 F7 N4 O4; Mol wt: 794.7643

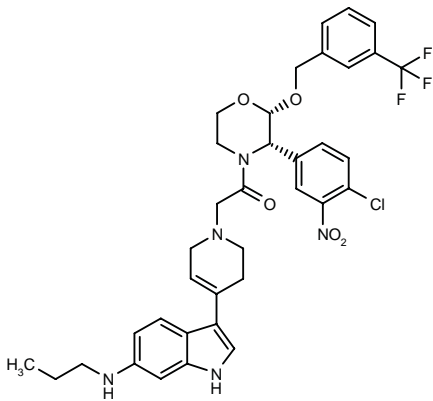
ACTION – Dual tachykinin receptor antagonist and 5-HT receptor agonist reported to be particularly useful for the treatment or prevention of pain and anxiety. A representative compound from a series of morpholinyl derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
275375	OPh	F	H	CF3	CF3	C ₄₀ H ₃₆ F ₇ N ₃ O ₄
275376	4-CF3-PhCONH	SO2Pr	H	CF3	CF3	C ₄₅ H ₄₃ F ₉ N ₄ O ₆ S
275377	4-i-Pr-PhCO	H	Ac	H	CH=CHMe	C ₄₇ H ₅₁ N ₃ O ₅



275374: C35 H32 F7 N3 O4



275378: C36 H37 Cl F3 N5 O5

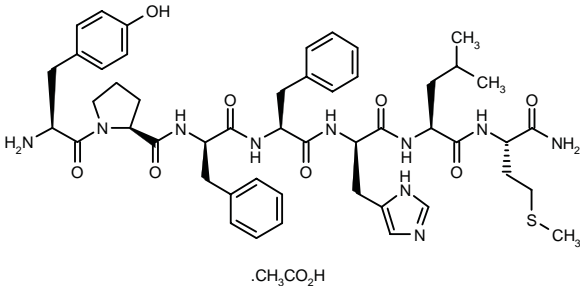
SOURCE – Lilly.

REFERENCES

1. Hipskind, P.A. and Lobb, K.L. (Eli Lilly and Company) *Morpholinyl tachykinin receptor antagonists*. US 5891875.

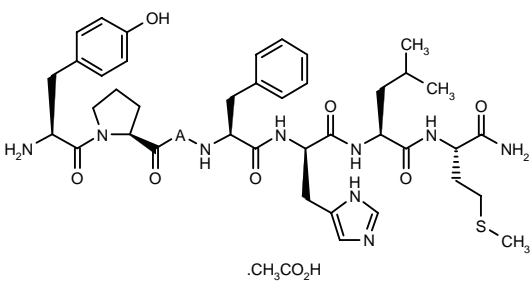
275418

L-Tyrosyl-L-prolyl-D-phenylalanyl-L-phenylalanyl-D-histidyl-L-leucyl-L-methioninamide acetate



C49 H64 N10 O8 S . C2 H4 O2; Mol wt: 1013.2240

ACTION – Opioid-like peptide with tachykinin NK₂ antagonist activity, as demonstrated in a binding assay by 69% inhibition of [¹²⁵I]-neurokinin A binding to human NK₂ receptors cloned in CHO cells at 1 μM. Other compounds from this series of opioid-like peptides include the following:



Compound	A	Formula
275419	-L-Phe-	C ₄₉ H ₆₄ N ₁₀ O ₈ S.C ₂ H ₄ O ₂
275420	-L-Trp-	C ₅₁ H ₆₆ N ₁₁ O ₈ S.C ₂ H ₄ O ₂

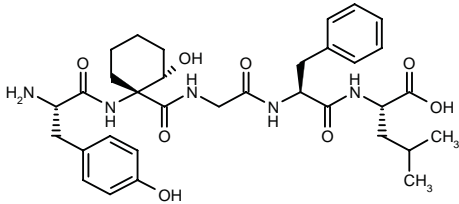
SOURCE – Asahi Glass.

REFERENCES

1. Sasaki, J. et al. (Asahi Glass Co., Ltd.) *Opioid-like peptides*. JP 99060598.

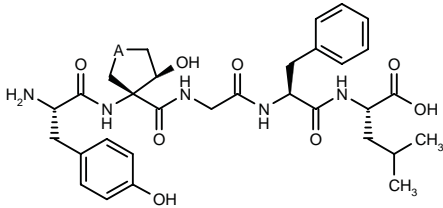
276468

N-[2(S)-Hydroxy-1(R)-(L-tyrosylamino)cyclohexyl-carbonyl]-glycyl-L-phenylalanyl-L-leucine

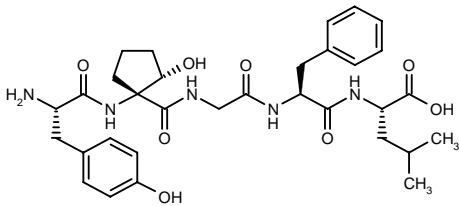


C33 H45 N5 O8; Mol wt: 639.7455

ACTION – Opioid analgesic agent with high affinity for μ- and δ-opioid receptors and low affinity for κ-opioid receptors, as demonstrated in binding assays by IC₅₀ values of 0.25, 0.01 and 6300 nM, respectively. Other exemplified enkephalin derivatives are:



Compound	A	Formula
276473	-CH2-	C ₃₂ H ₄₃ N ₅ O ₈
276474	-(CH2)2-	C ₃₃ H ₄₅ N ₅ O ₈



276471: C32 H43 N5 O8

SOURCE – Suntory.

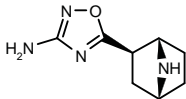
REFERENCES

1. Horikawa, M. et al. (Suntory Ltd.) *Enkephalin derivs. containing 1-amino-2-hydroxycycloalkan carboxylate*. JP 99080192.

CMI-1145

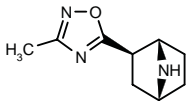
275310

exo-5-(7-Azabicyclo[2.2.1]hept-2-yl)-1,2,4-oxadiazol-3-amine



C8 H12 N4 O; Mol wt: 180.2098

ACTION – Antinociceptive agent, an analogue of epibatidine that elicits potent antinociceptive effects via activation of muscarinic M₄ receptors. In the mouse tail-flick test, compound at a dose of 30 mg/kg s.c. exerted potent antinociceptive activity while being devoid of toxic effects related to nonspecific nicotinic stimulation. Another compound from this series is:



CMI-936 [275309]: C9 H13 N3 O

SOURCE – VCB Research.

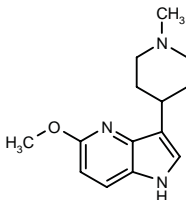
REFERENCES

1. Ellis, J.L. et al. *Development of muscarinic analgesics derived from epibatidine: Role of the M4 receptor subtype*. J Pharmacol Exp Ther 1999, 288(3): 1143.

ANTIMIGRAINE DRUGS

276646

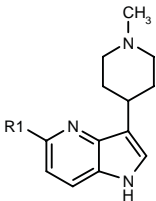
5-Methoxy-3-(1-methyl-4-piperidiny)-1*H*-pyrrolo[3,2-*b*]-pyridine



C14 H19 N3 O; Mol wt: 245.3241

ACTION – 5-ht_{1f} receptor agonist particularly useful for the treatment or prevention of migraine, but also potentially useful for other disorders linked to decreased 5-HT neurotransmission such as bulimia, depression, premenstrual syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, pain, posttraumatic syndrome, memory loss, aging-associated dementia, social phobia, attention

deficit hyperactivity disorder, obsessive–compulsive disorder, chronic fatigue syndrome, premature ejaculation, erectile dysfunction, anorexia nervosa, sleep disorders, autism and allergic rhinitis. Other exemplified pyrrolo-[3,2-*b*]pyridines include the following:



Compound	R1	Formula
276647	2-thienyl-CH2NH	C ₁₈ H ₂₂ N ₄ S
276649	CO2Me	C ₁₅ H ₁₉ N ₃ O ₂
276650	4-F-PhNHCO	C ₂₀ H ₂₁ FN ₄ O

SOURCE – Lilly.

REFERENCES

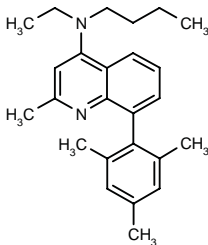
1. Filla, S.A. et al. (Eli Lilly and Company) *5-HT_{1F}-agonists effective in treating migraine*. US 5905084, WO 9925348.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

275244

N-Butyl-*N*-ethyl-2-methyl-8-(2,4,6-trimethylphenyl)-quinolin-4-amine



C25 H32 N2; Mol wt: 360.5418

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of stress-related disorders such as anxiety, depression, posttraumatic stress disorder, obsessive–compulsive disorder, headache, eating disorders, gastrointestinal disorders, irritable bowel syndrome, inflammatory diseases, immune suppression, hemorrhagic stress, drug and alcohol withdrawal symptoms and fertility problems. Other exemplified compounds from this series of quinoline and quinazoline derivatives include the following:

SOURCE – Suntory.

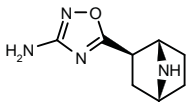
REFERENCES

1. Horikawa, M. et al. (Suntory Ltd.) *Enkephalin derivs. containing 1-amino-2-hydroxycycloalkan carboxylate*. JP 99080192.

CMI-1145

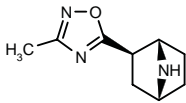
275310

exo-5-(7-Azabicyclo[2.2.1]hept-2-yl)-1,2,4-oxadiazol-3-amine



C8 H12 N4 O; Mol wt: 180.2098

ACTION – Antinociceptive agent, an analogue of epibatidine that elicits potent antinociceptive effects via activation of muscarinic M₄ receptors. In the mouse tail-flick test, compound at a dose of 30 mg/kg s.c. exerted potent antinociceptive activity while being devoid of toxic effects related to nonspecific nicotinic stimulation. Another compound from this series is:



CMI-936 [275309]: C9 H13 N3 O

SOURCE – VCB Research.

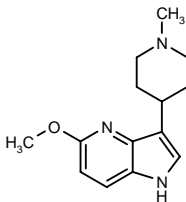
REFERENCES

1. Ellis, J.L. et al. *Development of muscarinic analgesics derived from epibatidine: Role of the M4 receptor subtype*. J Pharmacol Exp Ther 1999, 288(3): 1143.

ANTIMIGRAINE DRUGS

276646

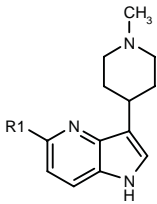
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276649	CO2Me	C ₁₅ H ₁₉ N ₃ O ₂
276650	4-F-PhNHCO	C ₂₀ H ₂₁ FN ₄ O

SOURCE – Lilly.

REFERENCES

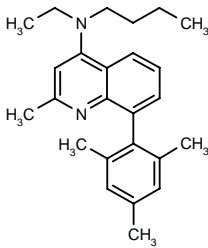
1. Filla, S.A. et al. (Eli Lilly and Company) *5-HT_{1F}-agonists effective in treating migraine*. US 5905084, WO 9925348.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

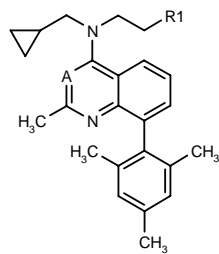
275244

N-Butyl-*N*-ethyl-2-methyl-8-(2,4,6-trimethylphenyl)-quinolin-4-amine



C25 H32 N2; Mol wt: 360.5418

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of stress-related disorders such as anxiety, depression, posttraumatic stress disorder, obsessive–compulsive disorder, headache, eating disorders, gastrointestinal disorders, irritable bowel syndrome, inflammatory diseases, immune suppression, hemorrhagic stress, drug and alcohol withdrawal symptoms and fertility problems. Other exemplified compounds from this series of quinoline and quinazoline derivatives include the following:



Compound	R1	A	Formula
275247	4-morpholinyl	CH	C ₂₉ H ₃₇ N ₃ O
275286	Me	N	C ₂₅ H ₃₁ N ₃

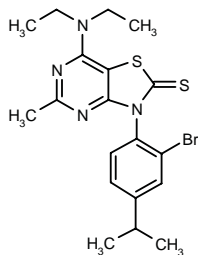
SOURCE – Duphar.

REFERENCES

1. Den Hartog, J.A.J. et al. (Duphar International Research BV) *Quinoline and quinazoline derivs. having corticotropin releasing factor (CRF) antagonist activity*. WO 9912908.

275578

3-[2-Bromo-4-(isopropyl)phenyl]-7-(diethylamino)-5-methyl-1,3-thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione



C19 H23 Br N4 S2; Mol wt: 451.4547

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist with high affinity for transfected human receptors expressed in HEK 293E cells (*K_i* = 4.1 nM). Potentially useful for the treatment of anxiety and depression.

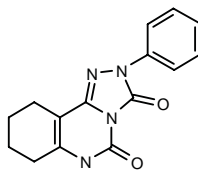
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Beck, J.P. et al. *Thiazolo[4,5-*d*]pyrimidine thiones and -ones as corticotropin-releasing hormone (CRH-R1) receptor antagonists*. Bioorg Med Chem Lett 1999, 9(8): 1185.

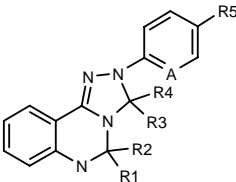
275872

2-Phenyl-2,3,5,6,7,8,9,10-octahydro[1,2,4]triazolo[4,3-*c*]quinazoline-3,5-dione

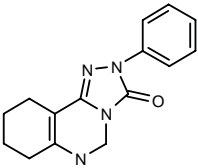


C15 H14 N4 O2; Mol wt: 282.3016

ACTION – Agent for the treatment of CNS disorders such as anxiety, epilepsy, sleep disorders and memory disorders with high affinity for the benzodiazepine binding site on the GABA_A receptor complex (*K_i* = 4.5 nM against [³H]-flumazenil binding in rat cortex preparations). Other compounds from this series of 1,2,4-triazolo[4,3-*c*]quinazolin-3-ones and 1,2,4-triazolo[4,3-*c*]quinazolin-3-thiones include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
275873		-O-		-O-	H	CH	C ₁₅ H ₁₀ N ₄ O ₂
275874	H	H		-O-	H	CH	C ₁₅ H ₁₂ N ₄ O
275875		-O-		-O-	H	N	C ₁₄ H ₉ N ₅ O ₂
275876	H	H		-O-	H	N	C ₁₄ H ₁₁ N ₅ O
275877	H	H		-O-	CH2N(Me)2	CH	C ₁₈ H ₁₉ N ₅ O
275878		-O-		-S-	H	CH	C ₁₅ H ₁₀ N ₄ OS



275879: C15 H16 N4 O

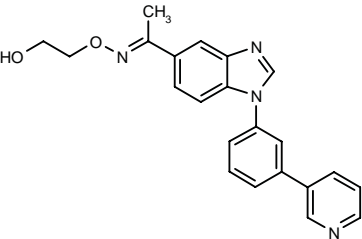
SOURCE – Neurogen.

REFERENCES

1. Chen, P. and Hutchison, A. (Neurogen Corp.) *Novel 1,2,4-triazolo[4,3-*c*]quinazolin-3-ones and 1,2,4-triazolo[4,3-*c*]quinazolin-3-thiones; a new class of GABA brain receptor ligands*. WO 9918106.

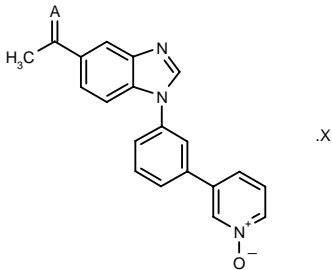
275944

1-[1-[3-(Pyridin-3-yl)phenyl]-1*H*-benzimidazol-5-yl]ethan-1-one *O*-(2-hydroxyethyl)oxime



C22 H20 N4 O2; Mol wt: 372.4260

ACTION – Anxiolytic agent and anticonvulsant with high affinity for the benzodiazepine site on the GABA_A receptor (*IC₅₀* = 4.2 nM). Other specifically claimed compounds from this series of benzimidazole derivatives include the following:



Compound	A	X	Formula
275945	N(OH)	HCl	C ₂₀ H ₁₆ N ₄ O ₂ ·HCl
275946	N(OEt)		C ₂₂ H ₂₀ N ₄ O ₂
275947	O		C ₂₀ H ₁₅ N ₃ O ₂

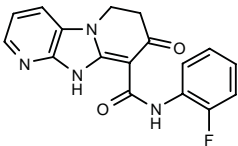
SOURCES – Meiji Seika; NeuroSearch.

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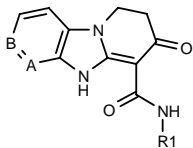
275977

N-(2-Fluorophenyl)-8-oxo-6,7,8,10-tetrahydridiprido-
[1,2-a:2',3'-d]imidazole-9-carboxamide



C17 H13 F N4 O2; Mol wt: 324.3137

ACTION – Anxiolytic agent, anticonvulsant, sedative/hypnotic and muscle relaxant that binds with high affinity to the benzodiazepine site on the GABA_A receptor. Within this series of dipyridoimidazole derivatives, the following are also specifically claimed:



Compound	R1	A	B	Formula
275979	Ph	N	CH	C ₁₇ H ₁₄ N ₄ O ₂
275981	4-Pyr	N	CH	C ₁₆ H ₁₃ N ₅ O ₂
275982	2,4,6-(F)3-Ph	N	CH	C ₁₇ H ₁₁ F ₃ N ₄ O ₂
275983	2,6-(F)2-Ph	N	CH	C ₁₇ H ₁₂ F ₂ N ₄ O ₂
275984	2,6-(F)2-Ph	CH	N	C ₁₇ H ₁₂ F ₂ N ₄ O ₂

SOURCE – Ortho-McNeil.

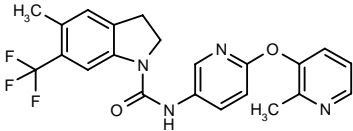
REFERENCES

1. Maryanoff, B.E. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Dipyridoimidazolderivs. useful in treating central nervous system disorders.* WO 9918105.

SB-243213*

260132

5-Methyl-N-[6-(2-methylpyridin-3-yloxy)pyridin-3-yl]-6-(trifluoromethyl)indoline-1-carboxamide



C22 H19 F3 N4 O2; Mol wt: 428.4121

ACTION – Selective 5-HT_{2C} antagonist with potential in the treatment of CNS disorders including anxiety and depression, currently undergoing phase I clinical trials.

SOURCE – SmithKline Beecham.

REFERENCES

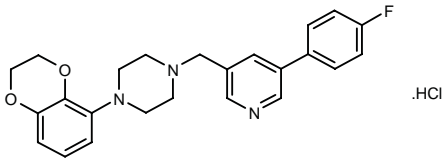
1. Blackburn, T.P. (SmithKline Beecham plc) *Pharmaceutical compsn. containing a 5HT2C antagonist and a D2 antagonist.* WO 9804289.
2. Bromidge, S.M. and Forbes, I.T. (SmithKline Beecham plc) *Indoline derivs. useful as 5-HT-2C receptor antagonists.* EP 912554, WO 9748699.
3. Lee, M.J. et al. *A preliminary study using fast gradient liquid chromatography coupled to a quadrupole orthogonal time-of-flight mass spectrometer.* Rapid Commun Mass Spectrom 1999, 13(4): 216.
4. *SmithKline Beecham provides update on product pipeline and future directions.* DailyDrugNews.com (Daily Essentials) 1998, April 21.
5. *SmithKline Beecham: annual report 1998/Q1 report 1999.* DailyDrugNews.com (Daily Essentials) 1999, April 27.

*Identified compound **260132** Drug Data Report 1998, 020(04): 0293.

ANTIPSYCHOTIC DRUGS

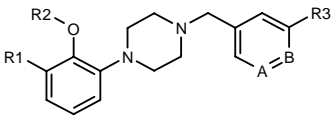
275032

1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[5-(4-fluorophen-yl)-3-pyridylmethyl]piperazine hydrochloride



C24 H24 F N3 O2 . HCl; Mol wt: 441.9315

ACTION – Antipsychotic agent with affinity for dopamine D₂ and D₄ and 5-HT_{1A} receptors, expected to induce less extrapyramidal side effects than available antipsychotic drugs due to its low propensity to induce catalepsy in rodents. Other compounds from this series of substituted pyridylmethylpiperazine derivatives include the following:



Compound	R1,R2	R3	A	B	Formula
275033	-NHCO-	4-F-Ph	CH	N	C ₂₃ H ₂₁ FN ₄ O ₂
275034	-OCH ₂ CH ₂ -	2-thienyl	N	CH	C ₂₂ H ₂₃ N ₃ O ₂ S

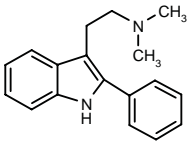
SOURCE – Duphar.

REFERENCES

1. Feenstra, R.W. et al. (Duphar International Research BV) *Substd. pyridylmethyl-piperazine and -piperidine derivs., their preparation and their use for treating central nervous system (CNS) disorders.* EP 908458.

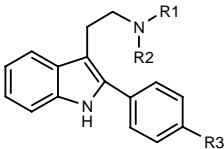
275171

N,N-Dimethyl-N-[2-(2-phenyl-1H-indol-3-yl)ethyl]amine



C18 H20 N2; Mol wt: 264.3700

ACTION – Antipsychotic agent with selective 5-HT_{2A} receptor-antagonist activity relative to the human dopamine D₂ receptor. Other specifically claimed phenylindole derivatives include the following:



Compound	R1	R2	R3	Formula
275172	Et	Et	H	C ₂₀ H ₂₄ N ₂
275173	-(CH ₂) ₄ -		H	C ₂₀ H ₂₂ N ₂
275174	-(CH ₂) ₅ -		H	C ₂₁ H ₂₄ N ₂
275175	-CH(Me)(CH ₂) ₄ -		H	C ₂₂ H ₂₅ FN ₂
275824	-(CH ₂) ₆ -		H	C ₂₂ H ₂₆ N ₂
275825	-CH ₂ CH ₂ OCH ₂ CH ₂ -		H	C ₂₀ H ₂₂ N ₂ O
275826	-(CH ₂) ₅ -		F	C ₂₁ H ₂₃ FN ₂

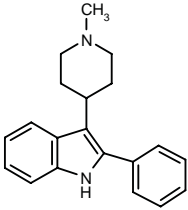
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Phenylindole derivs. as 5-HT_{2A} receptor ligands.* WO 9911619.

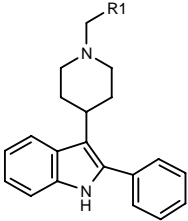
275209

3-(1-Methyl-4-piperidiny)-2-phenyl-1H-indole



C20 H22 N2; Mol wt: 290.4078

ACTION – Antipsychotic agent, a selective antagonist of human 5-HT_{2A} receptors (K_i < 100 nM in CHO cells) with reduced extrapyramidal side effects due to its lack of antagonism at dopamine D₂ receptors. Other representative compounds within this series of phenylindole derivatives include the following:



Compound	R1	Formula
275210	Ph	C ₂₆ H ₂₆ N ₂
275211	CH ₂ Ph	C ₂₇ H ₂₈ N ₂

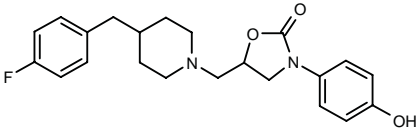
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Maxey, R.J. et al. (Merck Sharp & Dohme Ltd.) *Phenylindole derivs. as 5-HT_{2A} receptor antagonists.* WO 9911641.

275225

5-[4-(4-Fluorobenzyl)-1-piperidinylmethyl]-3-(4-hydroxyphenyl)oxazolidin-2-one



C22 H25 F N2 O3; Mol wt: 384.4485

ACTION – Antipsychotic agent with an improved profile of activity as compared to parent known compounds. It bound to the glutamate binding site on the NMDA receptor complex with an IC₅₀ of 0.01 μM using [³H]-ifenprodil as the ligand and was active *in vivo* in inhibiting apomorphine-induced stereotypy in rats (ED₅₀ = 2.8 mg/kg p.o.), without inducing catalepsy at 30 mg/kg s.c.

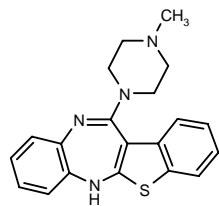
SOURCE – Merck KGaA.

REFERENCES

1. Prücher, H. et al. (Merck Patent GmbH) *Piperidinylmethyloxazolidinone deriv.* WO 9912924.

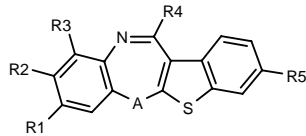
275913

12-(4-Methylpiperazin-1-yl)-6*H*-[1]benzothieno[2,3-*b*]-[1,5]benzodiazepine



C20 H20 N4 S; Mol wt: 348.4720

ACTION – Antipsychotic agent with potential in the treatment of both positive and negative symptoms of schizophrenia and reported to possess a low liability for side effects such as extrapyramidal motor disorders and granulocytopenia. Also reported to be useful for the treatment of Alzheimer’s disease and periodic psychosis. Other exemplified compounds from this series of fused thiophene derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
275914	H	Me	H	4-Me-1-Piz	H	NH	C ₂₁ H ₂₂ N ₄ S
275915	H	H	H	4-Me-1-Piz	OMe	NH	C ₂₁ H ₂₂ N ₄ OS
275916	F	H	H	NH2	OMe	NH	C ₁₆ H ₁₂ FN ₃ OS
275917	H	H	H	4-Me-1-Piz	F	NH	C ₂₀ H ₁₉ FN ₄ S
275918	F	F	H	4-Me-1-Piz	H	NH	C ₂₀ H ₁₈ F ₂ N ₄ S
275919	F	H	H	4-(t-BuOCO)-1-Piz	H	NH	C ₂₄ H ₂₅ FN ₄ O ₂ S
275920	F	H	OH	4-Me-1-Piz	H	NH	C ₂₀ H ₁₉ FN ₄ OS
275921	H	H	H	4-Me-1-Piz	H	O	C ₂₀ H ₁₉ N ₃ OS

SOURCE – Yoshitomi.

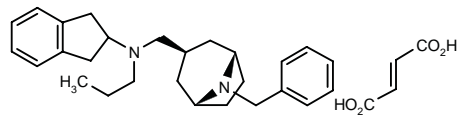
REFERENCES

1. Seio, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Fused thiophene cpds. and medicinal use thereof*. WO 9911647.

276124

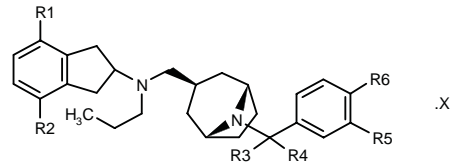
exo-N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-ylmethyl)-*N*-propyl-2,3-dihydro-1*H*-inden-2-amine fumarate

exo-N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-ylmethyl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-*N*-propylamine fumarate

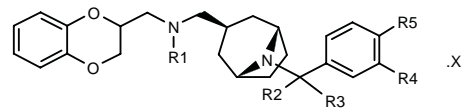


C27 H36 N2 . C4 H4 O4; Mol wt: 504.6670

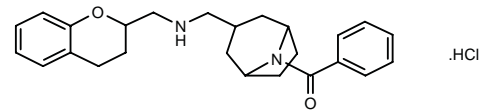
ACTION – Agent with strong affinity for dopamine D₃ and D₂ receptors and 5-HT_{1A} and 5-HT₂ receptors, potentially useful for the treatment of psychoses such as schizophrenia and extrapyramidal symptoms caused by neuroleptic agents, as well as for the treatment of anxiety, panic attacks, phobia, obsessive–compulsive disorders, depression, alcoholism, sexual dysfunction, eating disorders and migraine. Other exemplified compounds from this series of 8-azabicyclo[3.2.1]octane-3-methan-amine derivatives include the following:



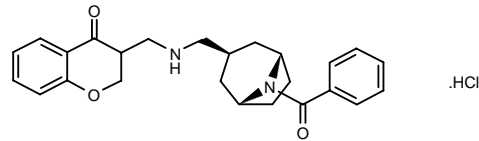
Compound	R1=R2	R3	R4	R5	R6	X	Formula
276125	H	H	H	H	Cl	fumarate	C ₂₇ H ₃₅ ClN ₂ .C ₄ H ₄ O ₄
276127	H	-O-		Cl	H	HCl	C ₂₇ H ₃₃ N ₂ O.HCl
276128	OMe	H	H	H	H	fumarate	C ₂₉ H ₄₀ N ₂ O ₂ .C ₄ H ₄ O ₄
276129	OMe	-O-		OEt	H	HCl	C ₃₁ H ₄₂ N ₂ O ₄ .HCl
276130	OMe	-O-		OMe	OMe	HCl	C ₃₁ H ₄₂ N ₂ O ₅ .HCl



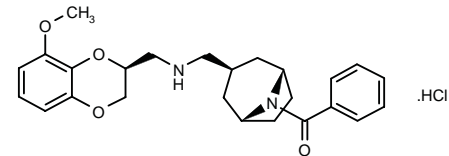
Compound	R1	R2	R3	R4	R5	X	Formula
276131	H	H	H	H	H	fumarate	C ₂₄ H ₃₀ N ₂ O ₂ .C ₄ H ₄ O ₄
276133	H	-O-		H	OMe	HCl	C ₂₅ H ₃₀ N ₂ O ₄ .HCl
276134	H	-O-		F	H	HCl	C ₂₄ H ₂₇ FN ₂ O ₃ .HCl
276135	H	H	H	F	H	fumarate	C ₂₄ H ₂₉ FN ₂ O ₂ .C ₄ H ₄ O ₄
276136	Pr	H	H	H	H	fumarate	C ₂₇ H ₃₈ N ₂ O ₂ .C ₄ H ₄ O ₄
276137	Pr	-O-		H	Me	HCl	C ₂₈ H ₃₆ N ₂ O ₃ .HCl



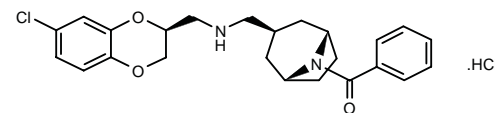
276138: C25 H30 N2 O2 . HCl



276139: C25 H28 N2 O3 . HCl



276140: C25 H30 N2 O4 . HCl



276141:C24 H27 Cl N2 O3 . HCl

SOURCE – Sanofi-Synthélabo.

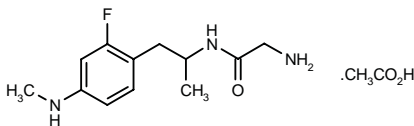
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ANTIDEPRESSANTS

275017

2-Amino-N-[2-[2-fluoro-4-(methylamino)phenyl]-1-methyl-ethyl]acetamide acetate



C12 H18 F N3 O . C2 H4 O2; Mol wt: 299.3438

M.p. 112-3 °C.

ACTION – Neuron-selective, reversible monoamine oxidase (MAO) inhibitor prodrug with 17-fold selectivity for MAO-A over MAO-B (IC₅₀ = 27 µM vs. > 100 µM in rat brain mitochondrial preparations). As a prodrug, it exhibited weak *in vitro* activity but strong and selective inhibition of neuronal monoaminergic deamination *ex vivo* in rats (ED₅₀ = 0.7-1.2 µmol/kg p.o.; extraneuronal ED₅₀ = 5.0-12 µmol/kg p.o.) when administered prior to phenelzine. Potentially useful as an antidepressant.

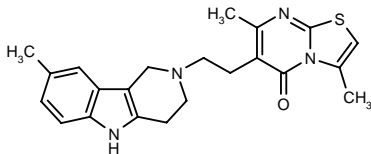
SOURCE – AstraZeneca.

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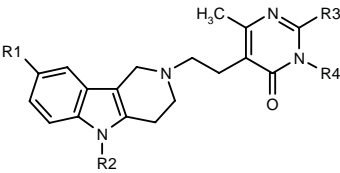
275248

3,7-Dimethyl-6-[2-(8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-2-yl)ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one



C22 H24 N4 O S; Mol wt: 392.5246

ACTION – Antidepressant with strong affinity for 5-HT receptors, particularly 5-HT₁ and 5-HT₂ receptors, with a pIC₅₀ value of 9.4 for binding to 5-HT₂ receptors in rat frontal cortex preparations using [³H]-ketanserin as the ligand. It also exhibited strong affinity for central α₂-adrenoceptors at concentrations of 1 µM or less in rat cortex preparations using [³H]-clonidine as the ligand. Also potentially useful as an anxiolytic and antipsychotic agent. Within this series of tetrahydro γ-carboline derivatives, the following are also included:



Compound	R1	R2	R3,R4	Formula
275250	F	H	-SCH=CH-	C ₂₀ H ₁₉ FN ₄ OS
275252	Cl	H	-CH=CHCH=CH-	C ₂₂ H ₂₁ ClN ₄ O
275253	Me	H	-SCH=CH-	C ₂₁ H ₂₂ N ₄ OS
275255	Cl	H	-SCH=C(Me)-	C ₂₁ H ₂₁ ClN ₄ OS
275257	Cl	H	-S(CH ₂) ₃ -	C ₂₁ H ₂₃ ClN ₄ OS
275259	F	4-F-Ph	-SCH ₂ CH ₂ -	C ₂₆ H ₂₄ F ₂ N ₄ OS

Certain compounds are also endowed with 5-HT reuptake-inhibitory activity and/or high affinity for dopamine receptors.

SOURCE – Janssen.

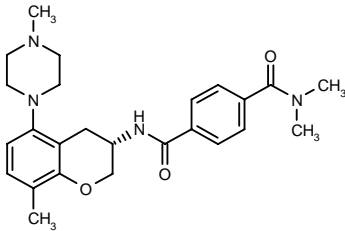
REFERENCES

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275509

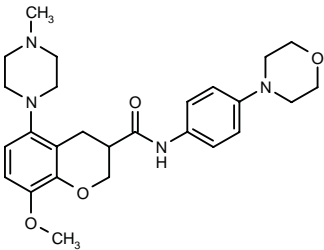
N¹,N¹-Dimethyl-N⁴-[8-methyl-5-(4-methyl-1-piperazinyl)-3,4-dihydro-2H-1-benzopyran-3(S)-yl]-1,4-benzene-dicarboxamide

N¹,N¹-Dimethyl-N⁴-[8-methyl-5-(4-methyl-1-piperazinyl)-3,4-dihydro-2H-1-benzopyran-3(S)-yl]terphthamide



C25 H32 N4 O3; Mol wt: 436.5528

ACTION – Agent for the treatment of CNS disorders such as depression with selective affinity for 5-HT_{1B} receptors and good oral bioavailability. Another specifically claimed substituted chroman derivative is:



275510: C26 H34 N4 O4

Compounds of the invention act preferably as antagonists at this receptor. Antagonists of terminal human 5-HT_{1B} autoreceptors are expected to increase synaptic 5-HT levels and enhance serotonergic transmission, resulting in an antidepressant effect.

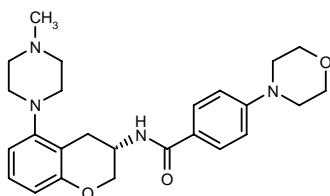
SOURCE – AstraZeneca.

REFERENCES

1. Berg, S. et al. (Astra AB) *Substd. chroman derivs.* WO 9914213.

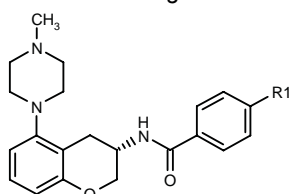
275511

N-[5-(4-Methyl-1-piperazinyl)-3,4-dihydro-2*H*-1-benzopyran-3(*S*)-yl]-4-(4-morpholinyl)benzamide



C₂₅ H₃₂ N₄ O₃; Mol wt: 436.5528

ACTION – Agent with selective affinity for 5-HT_{1B} (previously known as 5-HT_{1DB}) receptors, with potential in the treatment of a broad range of disorders including mood disorders, anxiety, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit hyperactivity disorder, migraine, memory disorders, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, pain, hypertension, urinary incontinence, vasospasm and cancer. Other compounds within this series of substituted chroman derivatives include the following:



Compound	R1	Formula
275512	1-Pip	C ₂₆ H ₃₄ N ₄ O ₂
275513	OBu	C ₂₅ H ₃₃ N ₃ O ₃
275514	CF ₃	C ₂₂ H ₂₄ F ₃ N ₃ O ₂
275515	N(Et) ₂	C ₂₅ H ₃₄ N ₄ O ₂
275516	OCF ₃	C ₂₂ H ₂₄ F ₃ N ₃ O ₃
275517	4-oxo-1-Pip	C ₂₆ H ₃₂ N ₄ O ₃
275518	5-oxo-perhydro-1,4-diazepin-1-yl	C ₂₆ H ₃₃ N ₅ O ₃
275519	4-PhCH ₂ -1-Piz	C ₃₂ H ₃₉ N ₅ O ₂

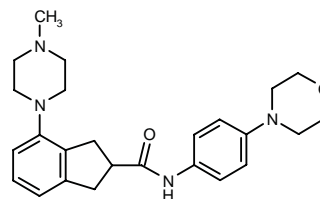
SOURCE – AstraZeneca.

REFERENCES

1. Berg, S. et al. (Astra AB) *Substd. chroman derivs.* WO 9914212.

275522

4-(4-Methyl-1-piperazinyl)-*N*-[4-(4-morpholinyl)phenyl]-indane-2-carboxamide



C₂₅ H₃₂ N₄ O₂; Mol wt: 420.5538

ACTION – Agent with selective affinity for the 5-HT_{1B} (previously known as 5-HT_{1DB}) receptor, with potential in the treatment of a broad range of disorders including mood disorders, anxiety, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit hyperactivity disorder, migraine, memory disorders, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, pain, hypertension, urinary incontinence, vasospasm and cancer. A representative compound from a series of substituted indane derivatives.

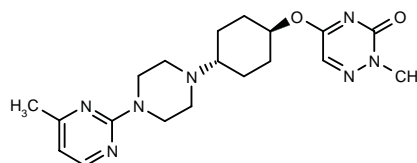
SOURCE – AstraZeneca.

REFERENCES

1. Berg, S. et al. (Astra AB) *Substd. indan derivs.* WO 9914207.

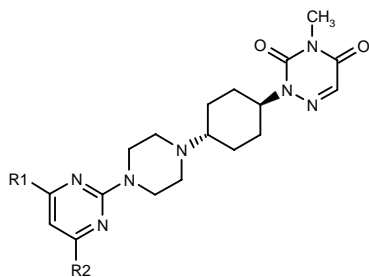
276177

trans-2-Methyl-5-[4-[4-(4-methylpyrimidin-2-yl)piperazin-1-yl]cyclohexyloxy]-1,2,4-triazin-3(2*H*)-one

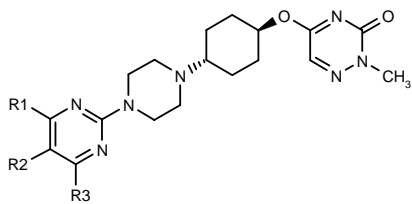


C₁₉ H₂₇ N₇ O₂; Mol wt: 385.4693

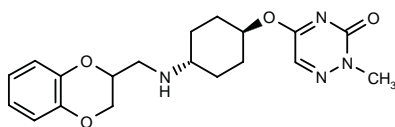
ACTION – 5-HT_{1A} receptor agonist with high affinity and selectivity, particularly as regards dopamine D₂ receptors and α₁-adrenoceptors, as demonstrated in binding assays by pK_i values of 9.60, < 5.0 and 5.95, respectively; it is more potent and selective than buspirone (pK_i = 7.65, 7.49 and 6.19, respectively) and flesinoxan (pK_i = 8.91, 7.05 and 6.50, respectively). *In vivo* in rats, it was capable of inducing the 5-HT syndrome characterized by reciprocal forepaw treading (ED₅₀ = 0.08 mg/kg p.o.; ED₅₀ buspirone = 20 mg/kg p.o.; ED₅₀ flesinoxan = 1.25 mg/kg p.o.), lower-lip retraction (ED₅₀ = 0.02 mg/kg p.o.; ED₅₀ buspirone = 2.5 mg/kg p.o.; ED₅₀ flesinoxan = 1.25 mg/kg p.o.) and flat body posture (ED₅₀ = 0.02 mg/kg i.p.; ED₅₀ buspirone > 40 mg/kg p.o.; ED₅₀ flesinoxan = 5 mg/kg p.o.). Antidepressant activity was demonstrated in the forced swimming test (ED₅₀ = 0.08 mg/kg p.o.; ED₅₀ buspirone > 160 mg/kg p.o.; ED₅₀ flesinoxan = 1.25 mg/kg p.o.). Also potentially useful in the treatment of anxiety, pain, neurodegenerative disorders, schizophrenia, Alzheimer's disease, sleep and eating disorders and cardiovascular and cerebrovascular disorders such as hypertension and migraine. Other compounds from this series of cyclohexane derivatives include the following:



Compound	R1	R2	Formula
276178	H	H	C ₁₈ H ₂₅ N ₇ O ₂
276179	Me	Me	C ₂₀ H ₂₉ N ₇ O ₂
276180	Me	H	C ₁₉ H ₂₇ N ₇ O ₂



Compound	R1	R2	R3	Formula
276181	H	H	H	C ₁₈ H ₂₅ N ₇ O ₂
276182	Me	H	Me	C ₂₀ H ₂₉ N ₇ O ₂
276183	Cl	H	H	C ₁₈ H ₂₄ ClN ₇ O ₂
276184	OMe	H	H	C ₁₉ H ₂₇ N ₇ O ₃
276185	CF ₃	H	H	C ₁₉ H ₂₄ F ₃ N ₇ O ₂
276186	H	F	H	C ₁₈ H ₂₄ FN ₇ O ₂



276187: C₁₉ H₂₄ N₄ O₄

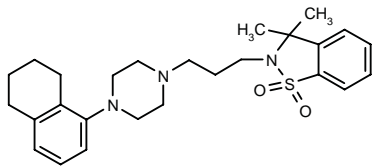
SOURCE – Pierre Fabre.

REFERENCES

1. Patoiseau, J.-F. et al. (Pierre Fabre Médicament) Cyclohexane derivs. difunctionalised in 1,4 as ligands of 5T H_{1A} receptors. WO 9920613.

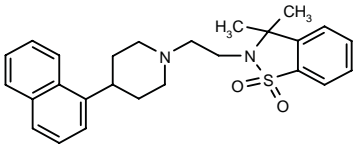
276242

3,3-Dimethyl-2-[3-[4-(5,6,7,8-tetrahydro-1-naphthalenyl)-1-piperazinyl]propyl]-2,3-dihydro-1H-1,2-benzisothiazole-S,S-dioxide



C₂₆ H₃₅ N₃ O₂ S; Mol wt: 453.6475

ACTION – Antidepressant, a 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist that displays high affinity and selectivity for the above receptors and additional 5-HT reuptake-inhibitory activity. Another representative compound from this series of 2-substituted 1,2-benzisothiazole derivatives is:



276243: C₂₆ H₃₀ N₂ O₂ S

SOURCE – BASF.

REFERENCES

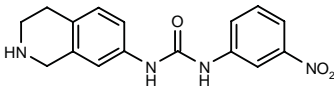
1. Libisch, W. et al. (BASF AG) 2-Substd. 1,2-benzisothiazole derivs. and their use as serotonin antagonists (5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D}). WO 9920616.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

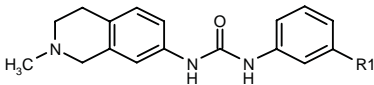
275503

N-(3-Nitrophenyl)-N'-(1,2,3,4-tetrahydro-7-isoquinol-1-yl)urea

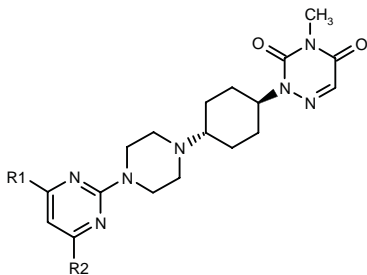


C₁₆ H₁₆ N₄ O₃; Mol wt: 312.3274

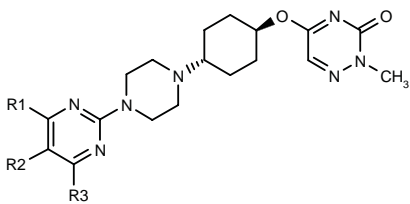
ACTION – Anticonvulsant also reported to be useful in the treatment or prevention of anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, Alzheimer's disease, Parkinson's disease, sleep disorders and traumatic brain injury. Compound exhibits high affinity for the [³H]-SB-204269-labeled binding site in rat forebrain membranes (pK_i > 8). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) test in mice, where it gave a 35% increase in seizure threshold at 10 mg/kg p.o. Other specifically claimed compounds from this series of substituted isoquinolines include the following:



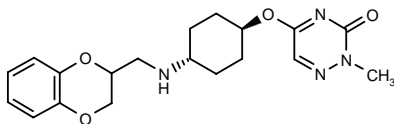
Compound	R1	Formula
275504	NO ₂	C ₁₇ H ₁₈ N ₄ O ₃
275505	CF ₃	C ₁₈ H ₁₈ F ₃ N ₃ O
275506	OMe	C ₁₈ H ₂₁ N ₃ O ₂
275507	Br	C ₁₇ H ₁₈ BrN ₃ O
275508	Cl	C ₁₇ H ₁₈ ClN ₃ O



Compound	R1	R2	Formula
276178	H	H	C ₁₈ H ₂₅ N ₇ O ₂
276179	Me	Me	C ₂₀ H ₂₉ N ₇ O ₂
276180	Me	H	C ₁₉ H ₂₇ N ₇ O ₂



Compound	R1	R2	R3	Formula
276181	H	H	H	C ₁₈ H ₂₅ N ₇ O ₂
276182	Me	H	Me	C ₂₀ H ₂₉ N ₇ O ₂
276183	Cl	H	H	C ₁₈ H ₂₄ ClN ₇ O ₂
276184	OMe	H	H	C ₁₉ H ₂₇ N ₇ O ₃
276185	CF ₃	H	H	C ₁₉ H ₂₄ F ₃ N ₇ O ₂
276186	H	F	H	C ₁₈ H ₂₄ FN ₇ O ₂



276187: C₁₉ H₂₄ N₄ O₄

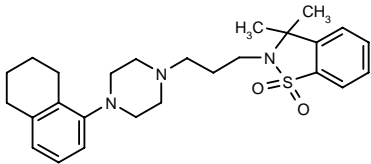
SOURCE – Pierre Fabre.

REFERENCES

1. Patoiseau, J.-F. et al. (Pierre Fabre Médicament) Cyclohexane derivs. difunctionalised in 1,4 as ligands of 5T H_{1A} receptors. WO 9920613.

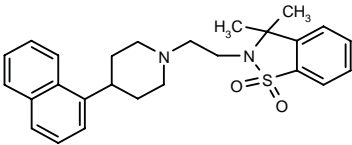
276242

3,3-Dimethyl-2-[3-[4-(5,6,7,8-tetrahydro-1-naphthalenyl)-1-piperazinyl]propyl]-2,3-dihydro-1H-1,2-benzisothiazole-S,S-dioxide



C₂₆ H₃₅ N₃ O₂ S; Mol wt: 453.6475

ACTION – Antidepressant, a 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist that displays high affinity and selectivity for the above receptors and additional 5-HT reuptake-inhibitory activity. Another representative compound from this series of 2-substituted 1,2-benzisothiazole derivatives is:



276243: C₂₆ H₃₀ N₂ O₂ S

SOURCE – BASF.

REFERENCES

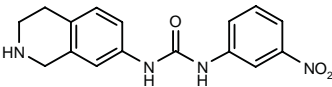
1. Libisch, W. et al. (BASF AG) 2-Substd. 1,2-benzisothiazole derivs. and their use as serotonin antagonists (5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D}). WO 9920616.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

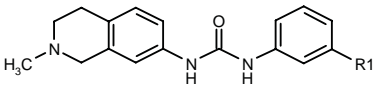
275503

N-(3-Nitrophenyl)-N'-(1,2,3,4-tetrahydro-7-isoquinol-1-yl)urea

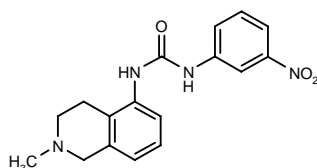


C₁₆ H₁₆ N₄ O₃; Mol wt: 312.3274

ACTION – Anticonvulsant also reported to be useful in the treatment or prevention of anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, Alzheimer's disease, Parkinson's disease, sleep disorders and traumatic brain injury. Compound exhibits high affinity for the [³H]-SB-204269-labeled binding site in rat forebrain membranes (pK_i > 8). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) test in mice, where it gave a 35% increase in seizure threshold at 10 mg/kg p.o. Other specifically claimed compounds from this series of substituted isoquinolines include the following:



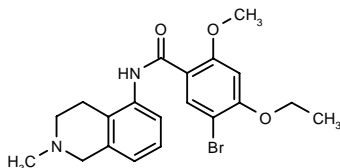
Compound	R1	Formula
275504	NO ₂	C ₁₇ H ₁₈ N ₄ O ₃
275505	CF ₃	C ₁₈ H ₁₈ F ₃ N ₃ O
275506	OMe	C ₁₈ H ₂₁ N ₃ O ₂
275507	Br	C ₁₇ H ₁₈ BrN ₃ O
275508	Cl	C ₁₇ H ₁₈ ClN ₃ O

**275586:** C₁₇ H₁₈ N₄ O₃**SOURCE** – SmithKline Beecham.**REFERENCES**

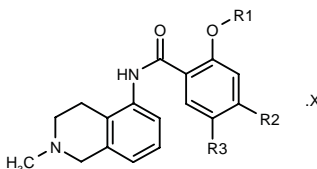
1. Thompson, M. and Porter, R.A. (SmithKline Beecham plc) *Substd. isoquinolines as anticonvulsants*. WO 9914197.

276513

5-Bromo-4-ethoxy-2-methoxy-*N*-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide

**C20** H₂₃ Br N₂ O₃; Mol wt: 419.3167

ACTION – Anticonvulsant that binds with high affinity to a novel receptor site labeled in rat brain by [³H]-SB-204269 and is active in the maximal electroshock seizure (MES) model in rats. It produced an increase of 403% in the seizure threshold in this model at 1 h following an oral dose of 2 mg/kg. Other exemplified substituted isoquinoline derivatives are:



Compound	R1	R2	R3	X	Formula
276514	Me	i-Pr	CN	HCl	C ₂₂ H ₂₅ N ₃ O ₂ .HCl
276515	Et	i-Pr	CF ₃		C ₂₃ H ₂₇ F ₃ N ₂ O ₂
276516	Et	i-Pr	CN	HCl	C ₂₃ H ₂₇ N ₃ O ₂ .HCl
276517	Me	OMe	CN	HCl	C ₂₀ H ₂₁ N ₃ O ₃ .HCl

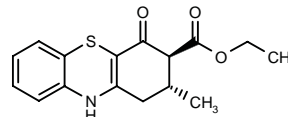
Compounds of the invention are also reported to be useful in the treatment and/or prevention of a wide range of CNS and neurological disorders including anxiety, depression, drug, nicotine and alcohol withdrawal, Parkinson's disease, migraine, cerebral ischemia, Alzheimer's disease, sleep disorders, traumatic brain injury, pain, multiple sclerosis and amyotrophic lateral sclerosis (ALS).

SOURCE – SmithKline Beecham.**REFERENCES**

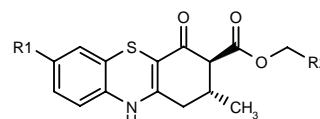
1. Thompson, M. et al. (SmithKline Beecham plc) *Substd. isoquinoline derivs. and their use as anticonvulsants*. WO 9921836.

276527

trans-2-Methyl-4-oxo-2,3,4,10-tetrahydro-1*H*-phenothiazine-3-carboxylic acid ethyl ester

**C16** H₁₇ N O₃ S; Mol wt: 303.3803

ACTION – Anticonvulsant expected to be particularly useful in the treatment of grand mal and partial seizures. *In vivo*, it showed anticonvulsant activity in the maximal electroshock (MES) test in rats at 30 mg/kg p.o. while exhibiting low toxicity in the rotarod assay in mice. Other exemplified phenothiazin-4-one derivatives include the following:



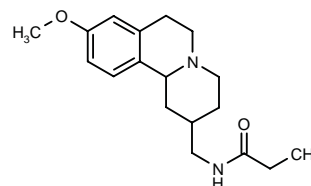
Compound	R1	R2	Formula
276528	H	H	C ₁₅ H ₁₅ NO ₃ S
276530	Cl	H	C ₁₅ H ₁₄ ClNO ₃ S
276531	Cl	Me	C ₁₆ H ₁₆ ClNO ₃ S
276532	Me	Me	C ₁₇ H ₁₉ NO ₃ S
276534	Br	H	C ₁₅ H ₁₄ BrNO ₃ S

SOURCE – Howard University, Washington, D.C. (US).**REFERENCES**

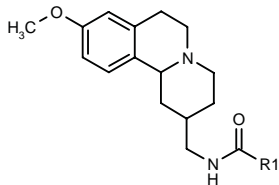
1. Scott, K.R. et al. *3-Carboalkoxy-2,3-dihydro-1H-phenothiazin-4[10H]-one derivs*. WO 9921560.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS**276491**

N-(9-Methoxy-2,3,4,6,7,11b-hexahydro-1*H*-benzo[*a*]-quinolizin-2-ylmethyl)propionamide

**C18** H₂₆ N₂ O₂; Mol wt: 302.4154

ACTION – α_2 -Adrenoceptor antagonist for the treatment of neurodegenerative disorders that is distinguished from other α_2 -adrenoceptor antagonists by its central activity, long duration of action and lack of effect on dopamine D₂ receptors. Due to its ability to release norepinephrine, it is expected to reactivate the intrinsic function of dopaminergic and cholinergic neurons and thereby stop or delay the progression of neurodegeneration. Potentially useful in the treatment of Parkinson's disease, Alzheimer's disease, Huntington's disease, cognitive and memory disorders, attention and vigilance deficits in the elderly, and cerebral ischemic and postischemic disorders. Other specifically claimed 2-aminomethylbenzo[a]quinolizidine derivatives include the following:



Compound	R1	Formula
276492	cyclohexyl	C ₂₂ H ₃₂ N ₂ O ₂
276493	i-Pr	C ₁₉ H ₂₈ N ₂ O ₂
276494	1-Ph-cyclopropyl	C ₂₈ H ₃₀ N ₂ O ₂
276495	CH ₂ Ph	C ₂₃ H ₂₈ N ₂ O ₂
276496	9H-9-fluorenyl	C ₂₉ H ₃₀ N ₂ O ₂
276497	CH ₂ CH ₂ Ph	C ₂₄ H ₃₀ N ₂ O ₂
276498	2-indanyl	C ₂₈ H ₃₀ N ₂ O ₂

SOURCE – Pierre Fabre.

REFERENCES

1. Mayer, P. et al. (Pierre Fabre Médicament) *Aminomethyl-benzo[a]quinolizidine derivs., preparation and therapeutic applications for neurodegenerative diseases*. WO 9921856.

PERSEPHIN

275656

Growth factor of the GDNF/neurturin family

ACTION – Growth factor of the GDNF (glial-derived neurotrophic factor)/neurturin family that promotes the survival and growth of neurons, as well as non-neuronal cells. Potentially useful for preventing atrophy, degeneration or death of certain cells, particularly neurons. A role for this growth factor in hematopoiesis, inflammation, allergy and cardiomyopathy is also suggested. Therapeutic or pharmaceutical compositions comprising persephin for the treatment of disorders including peripheral neuropathy, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, ischemic stroke, acute brain and spinal cord injury, multiple sclerosis, peripheral nerve trauma or injury, diabetes and renal dysfunction are claimed; particularly, its ability to promote mesencephalic cell survival indicates potential in the treatment of Parkinson's disease.

SOURCE – Washington University, St. Louis, MO (US).

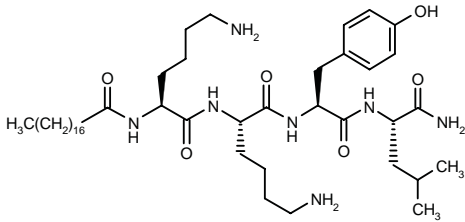
REFERENCES

1. Johnson, E.M. et al. (Washington University) *Persephin and related growth factors*. WO 9914235.

COGNITION-ENHANCING DRUGS

275827

Octadecenoyl-L-lysyl-L-lysyl-L-tyrosyl-L-leucinamide



C45 H81 N7 O6; Mol wt: 816.1779

ACTION – Neuroprotective agent, a 4-amino-acid sequence derived from the C-terminus of vasoactive intestinal peptide (VIP), proven to protect against β -amyloid peptide toxicity in newborn rat cerebral cortical neurons (EC₅₀ = 0.1 pM). Compound displaced [¹²⁵I]-VIP binding in astroglial cells (68% at 0.1 μ M). In a genetic model of Alzheimer's disease in ApoE-deficient animals, compound (1-4 μ g/day s.c. for 14 days) was shown to improve cognitive function and increase cortical choline acetyltransferase activity. Biodistribution studies following intranasal application of radiolabeled compound demonstrated intact peptide in the brain 30 min after nasal application.

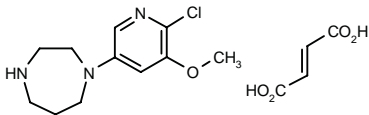
SOURCE – Yeda.

REFERENCES

1. Gozes, I. and Fridkin, M. (Yeda Research & Development Co. Ltd.) *Conjugates of lipophilic moieties and fragments of vasoactive intestinal peptide (VIP)*. WO 9740070.
2. Gozes, I. et al. *Mapping the active site in vasoactive intestinal to a core of four amino acids: Neuroprotective drug design*. Proc Natl Acad Sci USA 1999, 96(7): 4143.

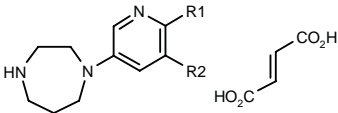
276669

1-(6-Chloro-5-methoxypyridin-3-yl)perhydro-1,4-diazepine fumarate

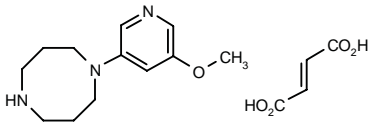


C11 H16 Cl N3 O . C4 H4 O4; Mol wt: 357.7920

ACTION – Neuronal nicotinic acetylcholine receptor (nAChR) ligand with potential in the treatment of Alzheimer’s disease, memory loss and dysfunction, senile and AIDS-related dementia, other neurodegenerative disorders such as Parkinson’s disease, CNS disorders such as schizophrenia, anxiety and depression, withdrawal from nicotine and other addictive substances, pain, inflammatory disorders and obesity. It gave IC₅₀ values for [³H]-cytisine (α4 and β2 subunits), [³H]-α-bungarotoxin (α7 and α1 subunits) and [³H]-epibatidine (α4/β2 subunit) binding of 0.0007, 0.005 and 0.90 μM, respectively. Other compounds from this series of heteroaryl diazacycloalkanes include the following:



Compound	R1	R2	Formula
276670	H	OMe	C ₁₁ H ₁₇ N ₃ O ₄
276673	-CH=CHCH=CH-		C ₁₄ H ₁₇ N ₃ ·C ₄ H ₄ O ₄
276674	Br	H	C ₁₀ H ₁₄ BrN ₃ ·C ₄ H ₄ O ₄
276675	H	OPr	C ₁₃ H ₂₁ N ₃ O ₄



276672: C12 H19 N3 O . C4 H4 O4

SOURCE – NeuroSearch.

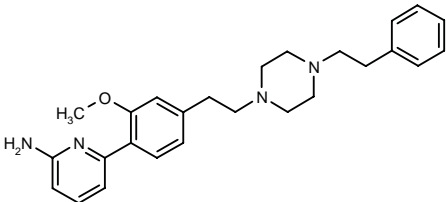
REFERENCES

1. Peters, D. et al. (NeuroSearch A/S) *Heteroaryl diazacycloalkanes as cholinergic ligands at nicotinic acetylcholine receptors*. WO 9921834.

TREATMENT OF
CEREBROVASCULAR DISEASES

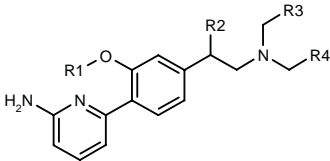
275057

6-[2-Methoxy-4-[2-[4-(2-phenylethyl)-1-piperazinyl]-ethyl]phenyl]pyridin-2-amine



C26 H32 N4 O; Mol wt: 416.5658

ACTION – Agent for the treatment of CNS disorders, inflammatory disorders and septic shock, an inhibitor of nitric oxide synthase (NOS) with IC₅₀ values of < 10 μM against both inducible and neuronal NOS. Other exemplified branched alkoxy-substituted 2-aminopyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
275058	i-Bu	H	-CH2N(CH2CH2Ph)CH2-		C ₂₉ H ₃₈ N ₄ O
275059	i-Bu	H	H	H	C ₁₉ H ₂₇ N ₃ O
275060	cyclopentyl-CH2	H	H	H	C ₂₁ H ₂₉ N ₃ O
275061	cyclopentyl-CH2	H	-CH2N(CH2CH2Ph)CH2-		C ₃₁ H ₄₀ N ₄ O
275062	i-Pr		-CH2-	i-Pr	C ₂₂ H ₃₁ N ₃ O

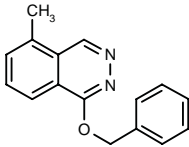
SOURCE – Pfizer.

REFERENCES

1. Lowe, J.A. III (Pfizer Products Inc.) *Branched alkoxy-subst. 2-aminopyridines as NOS inhibitors*. WO 9911620.

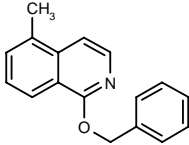
275115

1-Benzyloxy-5-methylphthalazine



C16 H14 N2 O; Mol wt: 250.2996

ACTION – Agent for the treatment of tissue damage resulting from cell damage or death due to necrosis or apoptosis, e.g., neurodegenerative disorders, inflammatory disorders and cancer. It acts by inhibiting poly(ADP-ribose) polymerase (PAPR, NAD⁺ ADP-ribosyltransferase), an enzyme that is thought to play a role in enhancing DNA repair but the excessive activation of which can rapidly lead to cell damage or death through depletion of energy stores. It was found to possess neuroprotective effects in a model of focal cerebral ischemia in rats. Another representative compound within this series of alkoxy-substituted derivatives is:



275116: C17 H15 N O

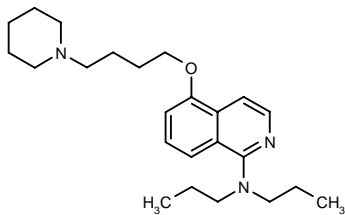
SOURCE – Guilford.

REFERENCES

1. Jackson, P.F. et al. (Guilford Pharmaceuticals Inc.) *Alkoxy-subst. cpds., methods, and compsns. for inhibiting PARP activity*. WO 9911628.

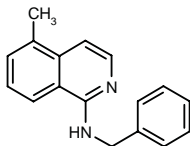
275117

N-[5-[4-(1-Piperidiny)butoxy]-1-isoquinolinyl]-N,N-dipropylamine



C24 H37 N3 O; Mol wt: 383.5763

ACTION – Agent for the treatment of tissue damage resulting from cell damage or death due to necrosis or apoptosis, e.g., neurodegenerative disorders, inflammatory disorders and cancer. It acts by inhibiting poly (ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase), an enzyme that is thought to play a role in enhancing DNA repair but the excessive activation of which can rapidly lead to cell damage or death through depletion of energy stores. It was found to possess neuroprotective effects in a model of focal cerebral ischemia in the rat. Another representative compound within this series of specifically claimed amino-substituted compounds is:



275118: C17H16N2

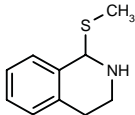
SOURCE – Guilford.

REFERENCES

1. Jackson, P.F. et al. (Guilford Pharmaceuticals Inc.) *Amino-substd. cpds., methods, and compsns. for inhibiting PARP activity.* WO 9911622.

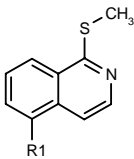
275119

1-(Methylsulfanyl)-1,2,3,4-tetrahydroisoquinoline

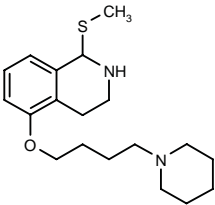


C10 H13 N S; Mol wt: 179.2857

ACTION – Agent for the treatment of tissue damage resulting from cell damage or death due to necrosis or apoptosis, e.g., neurodegenerative disorders, inflammatory disorders and cancer. It acts by inhibiting poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase), an enzyme that is thought to play a role in enhancing DNA repair but the excessive activation of which can rapidly lead to cell damage or death through depletion of energy stores. It was found to possess neuroprotective effects in a model of focal cerebral ischemia in rats. Other specifically claimed thioalkyl compounds include the following:



Compound	R1	Formula
275120	H	C ₁₀ H ₉ NS
275122	1-Pip-(CH ₂) ₄ O	C ₁₉ H ₂₆ N ₂ OS



275121: C19 H30 N2 O S

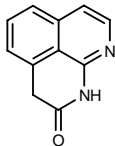
SOURCE – Guilford.

REFERENCES

1. Jackson, P.F. et al. (Guilford Pharmaceuticals Inc.) *Thioalkyl cpds., methods, and compsns. for inhibiting PARP activity.* WO 9911623.

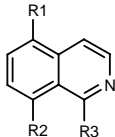
275123

2,3-Dihydro-1H-benzo[de][1,8]naphthyridin-2-one



C11 H8 N2 O; Mol wt: 184.1972

ACTION – Agent for the treatment of tissue damage resulting from cell damage or death due to necrosis or apoptosis, e.g., neurodegenerative disorders, inflammatory disorders and cancer. It acts by inhibiting poly(ADP-ribose) polymerase (PARP, NAP⁺ ADP-ribosyltransferase), an enzyme that is thought to play a role in enhancing DNA repair but the excessive activation of which can rapidly lead to cell damage or death through depletion of energy stores. It was found to possess neuroprotective effects in a model of focal cerebral ischemia in rats. Other specifically claimed di-N-heterocyclic derivatives include the following:



Compound	R1	R2,R3	Formula
275124	H	-CH(Me)CONH-	C ₁₂ H ₁₀ N ₂ O
275125	H	-CH(i-Pr)CONH-	C ₁₄ H ₁₄ N ₂ O
275126	H	-CH=N-	C ₁₀ H ₈ N ₂
275128	H	-C(Me)=N-	C ₁₁ H ₉ N ₂
275129	OH	-C(Me)=N-	C ₁₁ H ₈ N ₂ O

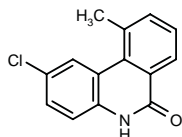
SOURCE – Guilford.

REFERENCES

1. Jackson, P.F. et al. (Guilford Pharmaceuticals Inc.) *Di-N-heterocyclic cpds., methods, and compsns. for inhibiting PARP activity*. WO 9911644.

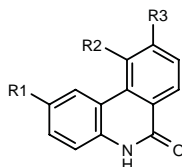
275130

2-Chloro-10-methylphenanthridin-6(5H)-one



C₁₄ H₁₀ Cl N O; Mol wt: 243.6920

ACTION – Agent for the treatment of tissue damage resulting from cell damage or death due to necrosis or apoptosis, e.g., neurodegenerative disorders, inflammatory disorders and cancer. It acts by inhibiting poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase), an enzyme that is thought to play a role in enhancing DNA repair but the excessive activation of which can rapidly lead to cell damage or death through depletion of energy stores. It was found to possess neuroprotective effects in a model of focal cerebral ischemia in rats. Other specifically claimed oxo-substituted derivatives include the following:



Compound	R1	R2	R3	Formula
275131	NO ₂	Me	H	C ₁₄ H ₁₀ N ₂ O ₃
275132	Cl	NH ₂	H	C ₁₃ H ₉ ClN ₂ O
275133	NO ₂	NH ₂	H	C ₁₃ H ₉ N ₃ O ₃
275134	Cl	NO ₂	H	C ₁₃ H ₇ ClN ₂ O ₃
275135	NO ₂	NO ₂	H	C ₁₃ H ₇ N ₃ O ₅
275136	Cl	OH	H	C ₁₃ H ₈ ClNO ₂
275137	NO ₂	OH	H	C ₁₃ H ₈ N ₂ O ₄
275138	Cl	Br	H	C ₁₃ H ₇ BrClNO
275139	NO ₂	Br	H	C ₁₃ H ₇ BrN ₂ O ₃
275141	Cl	NO	H	C ₁₃ H ₇ ClN ₂ O ₂
275142	Cl	-OCH ₂ O-		C ₁₄ H ₈ ClNO ₃
275143	NO ₂	-OCH ₂ O-		C ₁₄ H ₈ N ₂ O ₅

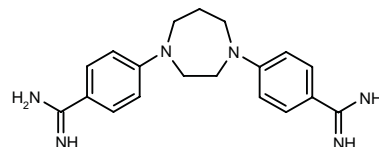
SOURCE – Guilford.

REFERENCES

1. Li, J.-H. et al. (Guilford Pharmaceuticals Inc.) *Oxo-substd. cpds., process of making, and compsns. and methods for inhibiting PARP activity*. WO 9911624.

276077

1,4-Bis(4-amidinophenyl)hexahydro-1,4-diazepine



C₁₉ H₂₄ N₆; Mol wt: 336.4406

ACTION – Noncompetitive NMDA receptor antagonist with binding affinity (IC₅₀ = 1.19 μM for inhibition of [³H]-dizolcypine binding in rat brain membranes) higher than pentamidine (IC₅₀ = 2.59 μM). Compound (1-10 μM) was able to inhibit NMDA- and glycine-induced increases in intracellular Ca²⁺ in cultured forebrain neurons from fetal rats, as well as to protect from glutamate-induced toxicity in cortical neurons, without causing any direct toxic effect. Potentially useful for the treatment of neurodegenerative states associated with cerebral ischemia, stroke, Alzheimer's disease and Huntington's disease.

SOURCES – University of Pittsburgh, Pittsburgh, PA (US); University of Tennessee, Memphis, TN (US); Xavier University of Louisiana, New Orleans, LA (US).

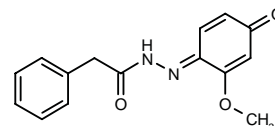
REFERENCES

1. Tan, B. et al. *Novel bisbenzamidines and bisbenzimidazolines as noncompetitive NMDA receptor antagonists*. Bioorg Med Chem Lett 1999, 9(9): 1299.

NG-061

274758

N'-(2-Methoxy-4-oxo-2,5-cyclohexadien-1-ylidene)-2-phenylacetohydrazide



C₁₅ H₁₄ N₂ O₃; Mol wt: 270.2866

Pale yellow crystals, m.p. 189-90 °C.

ACTION – Neurotrophic agent and nerve growth factor (NGF) potentiator, a fungal metabolite isolated from the fermentation broth of *Penicillium minioluteum* F-4627. It was shown to enhance (1-10 μg/ml) neurite outgrowth in rat pheochromocytoma PC12 cells, and its effects were potentiated in the presence of low concentrations of NGF. Compound did not increase survival in primary cultures of mouse cerebral cortical neurons subjected to hypoxic stress, and it was devoid of antimicrobial and antifungal activity.

SOURCE – Taisho.

REFERENCES

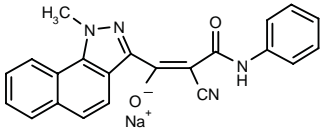
1. Bhandari, R. et al. *Structure of NG-061, a novel potentiator of nerve growth factor (NGF) isolated from Penicillium minioluteum F-4627.* J Antibiot 1999, 52(3): 231.

2. Ito, M. et al. *A novel fungal metabolite NG-061 enhances and mimics neurotrophic effect of nerve growth factor (NGF) on neurite outgrowth in PC12 cells.* J Antibiot 1999, 52(3): 224.

PNU-168754A

275813

2-Cyano-3-hydroxy-3-(1-methyl-1*H*-benzo[*g*]indazol-3-yl)-*N*-phenyl-2-propanamide sodium salt



C22 H15 N4 Na O2; Mol wt: 390.3765

ACTION – Kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor (IC₅₀ = 0.04 μM in rat liver mitochondrial preparations) with potential for the treatment or prevention of neurological disorders such as Alzheimer's disease, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia and hypoxia, spinal and head trauma, and epilepsy. A representative compound from a series of tricyclic 3-oxo-propanenitrile derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

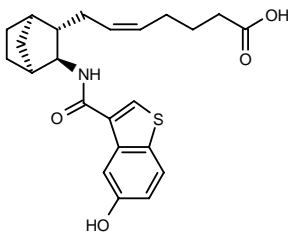
1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *Tricyclic 3-oxo-propanenitrile cpds.* WO 9916753.

RESPIRATORY DRUGS

**TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS**

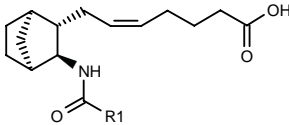
276229

(*Z*)-7-[(1*R*,2*S*,3*S*,4*S*)-3-(5-Hydroxy-1-benzothiophen-3-ylcarboxamido)bicyclo[2.2.1]hept-2-yl]hept-5-enoic acid

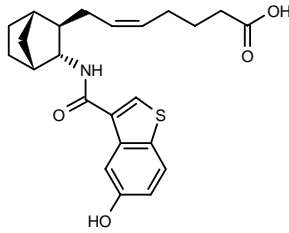


C23 H27 N O4 S; Mol wt: 413.5353

ACTION – Dual TxA₂ and PGD₂ antagonist that inhibited [³H]-PGD₂ binding in human platelet membrane fractions with an IC₅₀ of 0.0096 μM and the PGD₂-induced increase in human platelet cAMP levels with an IC₅₀ of 0.0039 μM; an IC₅₀ of 0.15 μM was obtained in an assay measuring TxA₂-antagonist activity. This compound inhibited antigen-induced nasal obstruction in sensitized guinea pigs by 74% following an oral dose of 30 mg/kg. Other representative compounds are:



Compound	R1	Formula
276230	7-benzothieryl	C ₂₃ H ₂₇ NO ₃ S
276231	3-benzothieryl	C ₂₃ H ₂₇ NO ₃ S
276232	5-F-3-benzothieryl	C ₂₃ H ₂₆ FNO ₃ S
276233	6-OH-3-benzothieryl	C ₂₃ H ₂₇ NO ₄ S



276234: C23 H27 N O4 S

SOURCE – Shionogi.

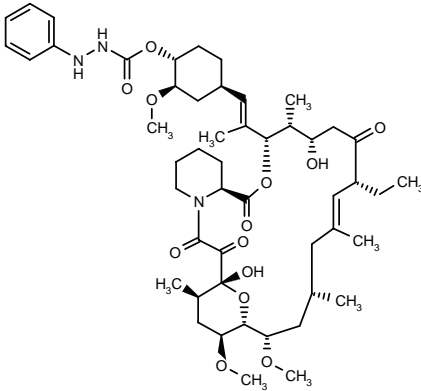
REFERENCES

1. Honma, T. (Shionogi & Co. Ltd.) *Cpds. having [2.2.1]bicyclo skeleton.* WO 9915502.

ASTHMA THERAPY

272002

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14-dihydroxy-23,25-dimethoxy-12-[2(*E*)-[3-methoxy-4-(3-phenylcarbazoyloxy)cyclohexyl]-1-methylvinyl]-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraene



C50 H75 N3 O13; Mol wt: 926.1505

SOURCE – Taisho.

REFERENCES

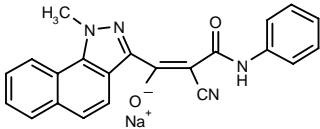
1. Bhandari, R. et al. *Structure of NG-061, a novel potentiator of nerve growth factor (NGF) isolated from Penicillium minioluteum F-4627.* J Antibiot 1999, 52(3): 231.

2. Ito, M. et al. *A novel fungal metabolite NG-061 enhances and mimics neurotrophic effect of nerve growth factor (NGF) on neurite outgrowth in PC12 cells.* J Antibiot 1999, 52(3): 224.

PNU-168754A

275813

2-Cyano-3-hydroxy-3-(1-methyl-1*H*-benzo[*g*]indazol-3-yl)-*N*-phenyl-2-propanamide sodium salt



C22 H15 N4 Na O2; Mol wt: 390.3765

ACTION – Kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor (IC₅₀ = 0.04 μM in rat liver mitochondrial preparations) with potential for the treatment or prevention of neurological disorders such as Alzheimer's disease, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia and hypoxia, spinal and head trauma, and epilepsy. A representative compound from a series of tricyclic 3-oxo-propanenitrile derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

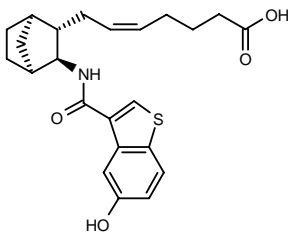
1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *Tricyclic 3-oxo-propanenitrile cpds.* WO 9916753.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

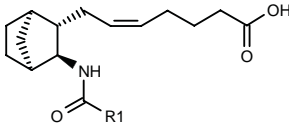
276229

(*Z*)-7-[(1*R*,2*S*,3*S*,4*S*)-3-(5-Hydroxy-1-benzothiophen-3-ylcarboxamido)bicyclo[2.2.1]hept-2-yl]hept-5-enoic acid

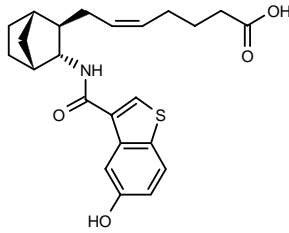


C23 H27 N O4 S; Mol wt: 413.5353

ACTION – Dual TxA₂ and PGD₂ antagonist that inhibited [³H]-PGD₂ binding in human platelet membrane fractions with an IC₅₀ of 0.0096 μM and the PGD₂-induced increase in human platelet cAMP levels with an IC₅₀ of 0.0039 μM; an IC₅₀ of 0.15 μM was obtained in an assay measuring TxA₂-antagonist activity. This compound inhibited antigen-induced nasal obstruction in sensitized guinea pigs by 74% following an oral dose of 30 mg/kg. Other representative compounds are:



Compound	R1	Formula
276230	7-benzothieryl	C ₂₃ H ₂₇ NO ₃ S
276231	3-benzothieryl	C ₂₃ H ₂₇ NO ₃ S
276232	5-F-3-benzothieryl	C ₂₃ H ₂₆ FNO ₃ S
276233	6-OH-3-benzothieryl	C ₂₃ H ₂₇ NO ₄ S



276234: C23 H27 N O4 S

SOURCE – Shionogi.

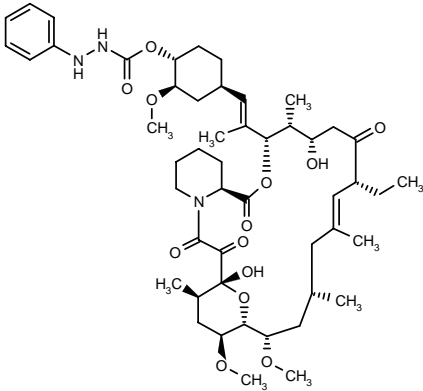
REFERENCES

1. Honma, T. (Shionogi & Co. Ltd.) *Cpds. having [2.2.1]bicyclo skeleton.* WO 9915502.

ASTHMA THERAPY

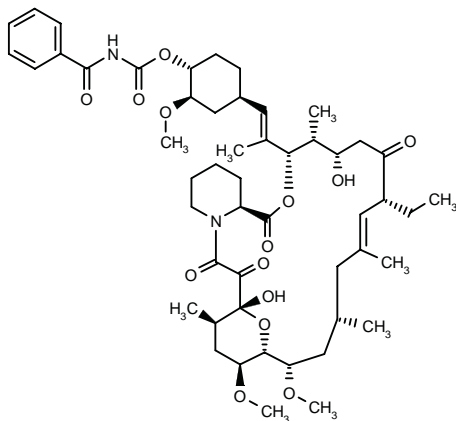
272002

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*R*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-17-Ethyl-1,14-dihydroxy-23,25-dimethoxy-12-[2(*E*)-[3-methoxy-4-(3-phenylcarbazoyloxy)cyclohexyl]-1-methylvinyl]-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraene



C50 H75 N3 O13; Mol wt: 926.1505

ACTION – Immunosuppressant, an analogue of ascomycin that in models of *in vitro* T-cell activation such as the IL-2 reporter gene assay, the murine mixed lymphocyte reaction (MLR) and the FKBP-12-binding assay exhibited nanomolar IC₅₀ values similar or superior to those of the parent compound and tacrolimus (FK-506). Potentially useful in the treatment of chronic inflammatory diseases of the airways such as asthma. Another ascomycin analogue is:



272001: C51 H74 N2 O14

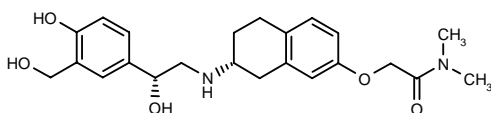
SOURCE – Novartis.

REFERENCES

1. Hersperger, R. et al. *Preparation and immunosuppressive activity of 32-(O)-acylated and 32-(O)-thioacylated analogues of ascomycin*. Bioorg Med Chem Lett 1999, 9(2): 227.

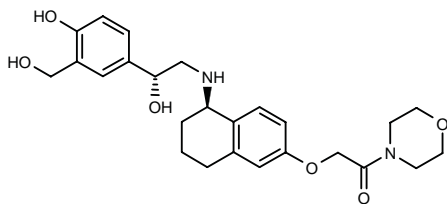
275064

2-[7(*R*)-[2(*R*)-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethylamino]-5,6,7,8-tetrahydro-2-naphthalenyloxy]-*N,N*-dimethylacetamide

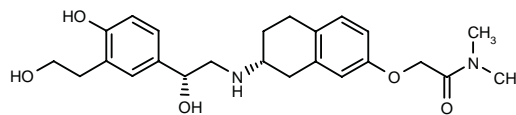


C23 H30 N2 O5; Mol wt: 414.4990

ACTION – Bronchodilating agent giving an EC₅₀ of 0.25 nM for relaxing histamine-contracted guinea pig tracheal tissue whereas the concentration capable of increasing heart rate in isolated guinea pig atria by 20% was 7.8 nM. Other representative compounds within this series of phenylethanolaminotetralin derivatives include the following:



275065: C25 H32 N2 O6



275067: C24 H32 N2 O5

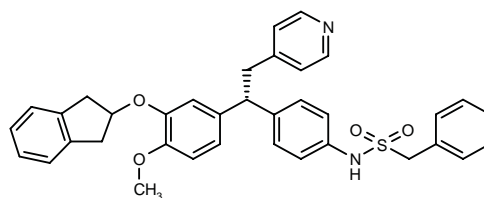
SOURCE – Kissei.

REFERENCES

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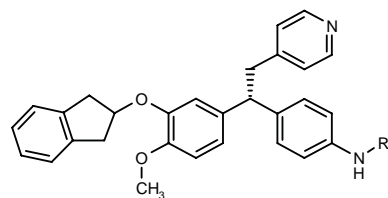
275340

N-[4-[1(*R*)-[3-(2-Indanyloxy)-4-methoxyphenyl]-2-(4-pyridinyl)ethyl]phenyl]benzylsulfonamide



C36 H34 N2 O4 S; Mol wt: 590.7406

ACTION – Antiasthmatic, antiallergic and antiinflammatory agent, a potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 2.0 nM) with little or no activity against other PDE isozymes at concentrations up to 100 μM. Compound exhibits greatly improved metabolic stability in cultured rat hepatocytes (> 80% unmetabolized compound after culturing for 3 h) compared to structurally related compounds which are extensively metabolized. Other specifically claimed compounds within this series of trisubstituted phenyl derivatives are:



Compound	R1	Formula
275341	H	C ₂₉ H ₂₈ N ₂ O ₂
275343	CONH ₂	C ₃₂ H ₃₃ N ₃ O ₃

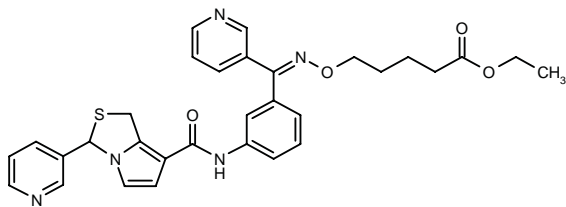
SOURCE – Celltech.

REFERENCES

1. Warrellow, G.J. and Brown, J.A. (Celltech Therapeutics Ltd.) *Tri-substd. phenyl derivs. useful as PDE IV inhibitors*. US 5891896.

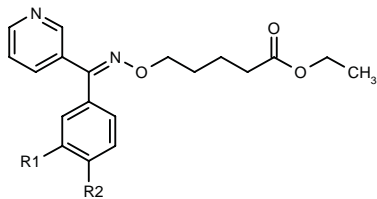
275400

(E)-5-[1-(3-Pyridinyl)-1-[3-[3-(3-pyridinyl)-1 H-pyrrolo-[1,2-c]thiazol-7-ylcarboxamido]phenyl]methyleneaminoxy]pentanoic acid ethyl ester

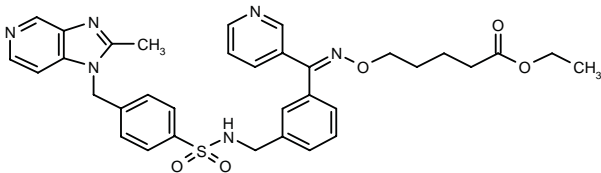


C31 H31 N5 O4 S; Mol wt: 569.6829

ACTION – Antiallergic and antiinflammatory agent, a dual PAF antagonist and TxA₂ synthase inhibitor. *In vitro*, compound gave 78.8% inhibition of PAF-induced aggregation of rabbit platelet-rich plasma (PRP) at 1 μM, and 95.0% inhibition of TxB₂ production in human platelet microsomes at 0.1 μM. Within this series of substituted methyleneaminoxyalkanoic acid derivatives, the following are also included:



Compound	R1	R2	Formula
275401	H	4-[2-(3-Pyr)-4-thiazol-idinyl-CO]-1-Piz-CH2	C ₃₃ H ₄₀ N ₆ O ₄ S
275402	2-(3-Pyr)-4-thiazol-idinyl-CONH	H	C ₂₈ H ₃₁ N ₅ O ₄ S
275404	1-[EtOCO(CH2)4]-6-indolyl-OCH2	H	C ₃₅ H ₄₁ N ₃ O ₆



275403: C34 H36 N6 O5 S

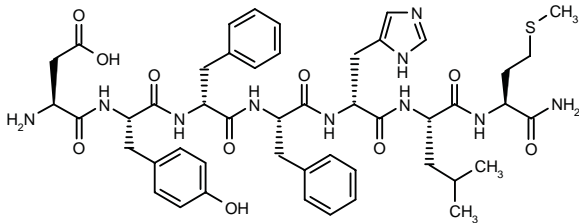
SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, S. et al. (Nikken Chemicals Co., Ltd.) *Substd. aminoxy alkanic acid derivs.* JP 99060570.

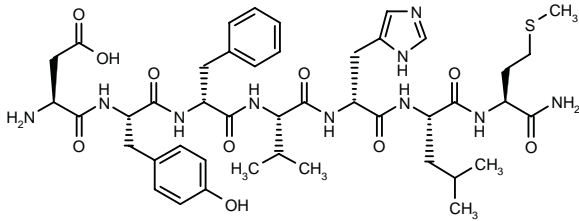
275421

L-Aspartyl-L-tyrosyl-D-phenylalanyl-L-phenylalanyl-D-histidyl-L-leucyl-L-methioninamide



C48 H62 N10 O10 S; Mol wt: 971.1438

ACTION – Tachykinin antagonist with affinity for NK₁ and NK₂ receptors. Another exemplified compound from this series of peptides is:



275422: C44 H62 N10 O10 S

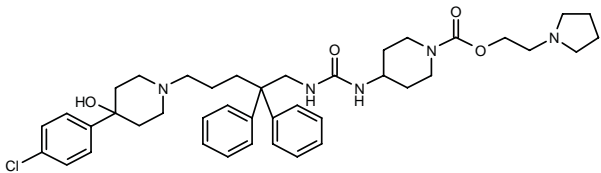
SOURCE – Asahi Glass.

REFERENCES

1. Sasaki, J. et al. (Asahi Glass Co., Ltd.) *Peptides.* JP 99060597.

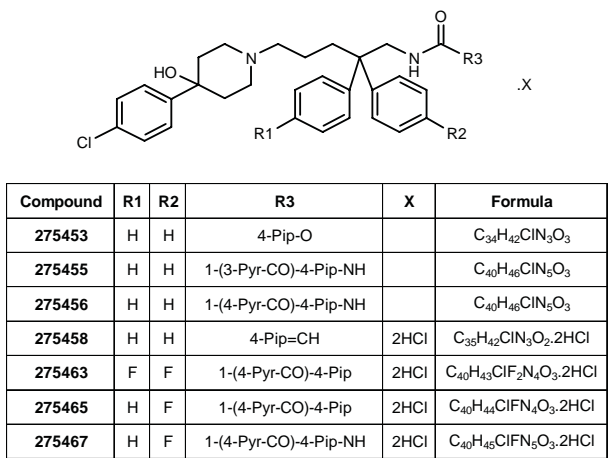
275450

4-[3-[5-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-2,2-diphenylpentyl]ureido]piperidine-1-carboxylic acid 2-(1-pyrrolidinyl)ethyl ester



C41 H54 Cl N5 O4; Mol wt: 716.3616

ACTION – Agent for the treatment of allergic and inflammatory disorders and multiple sclerosis, a dual MIP-1α (macrophage inflammatory protein-1α)/RANTES (Regulated on Activation, Normal T Expressed and Secreted) receptor antagonist that displayed an IC₅₀ value of 0.01 μM against [¹²⁵I]-RANTES binding to the human RANTES receptor expressed in CHO cells. Other exemplified compounds from this series of 4-hydroxy-piperidine derivatives include the following:



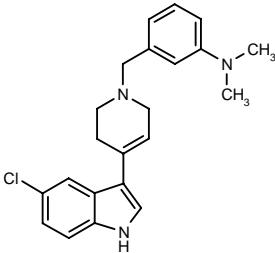
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Hydroxypiperidine cpds. and their agents*. JP 99071350.

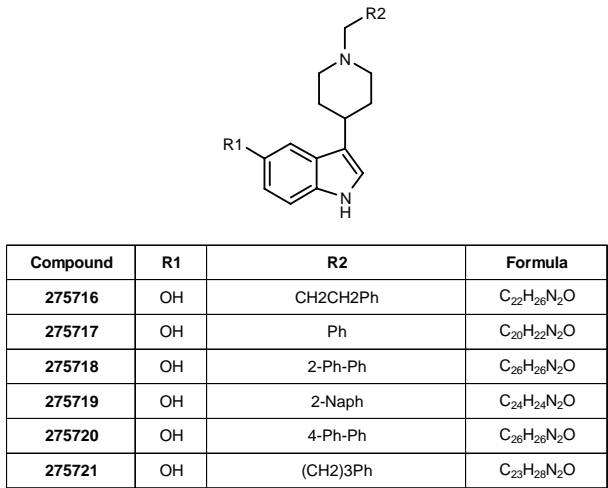
275714

N-[3-[4-(5-Chloro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]phenyl]-N,N-dimethylamine

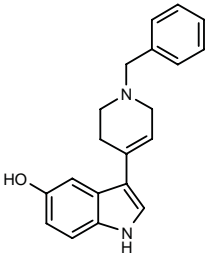


C22 H24 Cl N3; Mol wt: 365.9056

ACTION – Chemokine CCR5 receptor modulator (agonist or antagonist) with potential in the treatment or prevention of CCR5-mediated diseases such as asthma and allergic diseases, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease and HIV infection. Within this series of 3-(4-piperidiny)indoles, the following are also specifically claimed:



Compound	R1	R2	Formula
275722	OH	CH2CH(Ph)2	C28H30N2O
275723	OH	4-t-Bu-Ph	C24H30N2O
275724	OH	2H-benzotriazol-2-yl-(CH2)3	C23H27N5O
275725	OH	1H-benzotriazol-1-yl-(CH2)3	C23H27N5O
275726	OH	CH2CH=C(Ph)2	C29H30N2O
275727	OH	CH=C(Ph)2	C28H28N2O
275728	H	CH2CH(Ph)2	C28H30N2



275715: C20 H20 N2 O

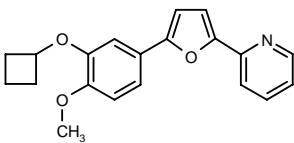
SOURCE – SmithKline Beecham.

REFERENCES

1. Bondinell, W.E. et al. (SmithKline Beecham Corp.;SmithKline Beecham plc) *Cpds. and methods*. WO 9917773.

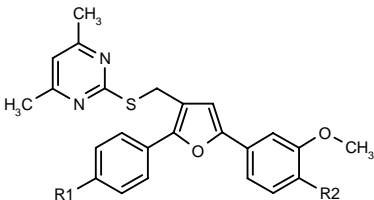
275848

2-[5-(3-Cyclobutoxy-4-methoxyphenyl)furan-2-yl]pyridine

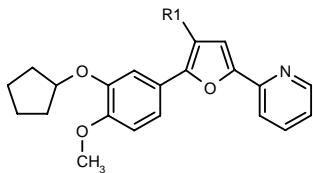


C20 H19 N O3; Mol wt: 321.3741

ACTION – Antiasthmatic and antiinflammatory agent that acts by selectively inhibiting phosphodiesterase type 4 (PDE4), thus resulting in an elevation of cAMP levels, and which is reported to be devoid of the side effects associated with known PDE4 inhibitors such as rolipram. Other specifically claimed compounds from this series of arylfuran derivatives include the following:



Compound	R1	R2	Formula
275849	CO2H	H	C25H22N2O4S
275850	CH(Me)2OH	H	C27H28N2O3S
275851	CO2H	OMe	C26H24N2O5S



Compound	R1	Formula
275852	Br	C ₂₁ H ₂₀ BrNO ₃
275853	CH(OH)Ph	C ₂₈ H ₂₇ NO ₄
275854	COPh	C ₂₈ H ₂₅ NO ₄

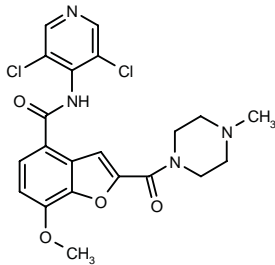
SOURCE – Merck Frosst.

REFERENCES

1. Perrier, H. et al. (Merck Frosst Canada Inc.) *Aryl furan derivs. as PDE IV inhibitors.* WO 9918095.

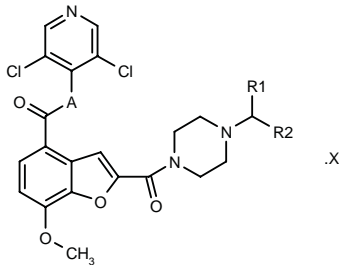
276205

N-(3,5-Dichloropyridin-4-yl)-7-methoxy-2-(4-methyl-piperazin-1-ylcarbonyl)-1-benzofuran-4-carboxamide



C₂₁ H₂₀ Cl₂ N₄ O₄; Mol wt: 463.3190

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with low emetogenic potential. Compound induced 25% inhibition of recombinant human PDE4 at 10 nM and 75% inhibition at 0.1 μM; it also induced 68% inhibition of lipopolysaccharide-stimulated tumor necrosis factor (TNF-α) production in mice at a dose of 30 mg p.o. Other representative compounds from this series of benzofuran derivatives include the following:



Compound	R1	R2	A	X	Formula
276206	CH ₂ OH	H	NH		C ₂₂ H ₂₂ Cl ₂ N ₄ O ₅
276207	CH ₂ OH	Et	NH		C ₂₄ H ₂₆ Cl ₂ N ₄ O ₅
276208	H	H	CH ₂		C ₂₂ H ₂₁ Cl ₂ N ₃ O ₄
276209	CH ₂ OH	H	CH ₂		C ₂₃ H ₂₃ Cl ₂ N ₃ O ₅
276210	Me	H	CH ₂	fumarate	C ₂₃ H ₂₃ Cl ₂ N ₃ O ₄ ·C ₄ H ₄ O ₄
276211	Me	Me	CH ₂	fumarate	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₄ ·C ₄ H ₄ O ₄
276213	CH ₂ OEt	H	CH ₂	fumarate	C ₂₅ H ₂₇ Cl ₂ N ₃ O ₅ ·C ₄ H ₄ O ₄
276214	CH ₂ OH	Me	CH ₂		C ₂₄ H ₂₅ Cl ₂ N ₃ O ₅
276215	CH ₂ OH	Et	CH ₂		C ₂₅ H ₂₇ Cl ₂ N ₃ O ₅

SOURCE – Kyowa Hakko.

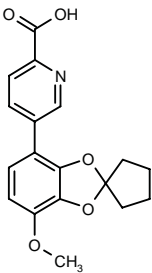
REFERENCES

1. Ohshima, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Benzofuran derivs.* WO 9916768.

276216

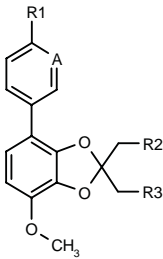
5-(7-Methoxy-2,2-tetramethylene-1,3-benzodioxol-4-yl)-pyridine-2-carboxylic acid

5-(7-Methoxyspiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl)pyridine-2-carboxylic acid



C₁₈ H₁₇ N O₅; Mol wt: 327.3343

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor found to potently inhibit the production of tumor necrosis factor (TNF-α) induced by lipopolysaccharide (LPS) in mice (100% inhibition at 10 mg/kg p.o.); it showed a low liability for inducing emesis. Other representative compounds from this series of benzodioxole derivatives include the following:



Compound	R1	R2	R3	A	Formula
276217	CO ₂ H	H	H	CH	C ₁₇ H ₁₆ O ₅
276218	Me	-(CH ₂) ₂ -		N	C ₁₈ H ₁₉ NO ₃

SOURCE – Kyowa Hakko.

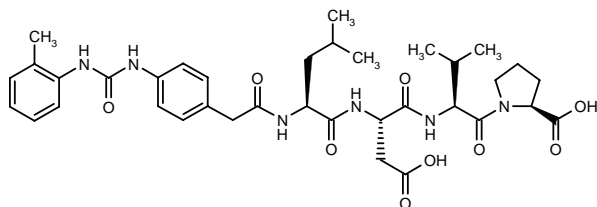
REFERENCES

1. Ohshima, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Benzodioxole derivs.* WO 9916766.

BIO-1211

274429

N-[4-[3-(2-Methylphenyl)ureido]phenylacetyl]-L-leucyl-L-aspartyl-L-valyl-L-proline



C36 H48 N6 O9; Mol wt: 708.8082

Fine white powder, m.p. 175-8 °C (decomp.).

ACTION – Potent and selective integrin $\alpha_4\beta_1$ receptor antagonist (IC_{50} = 1 nM in a binding assay; IC_{50} = 4 nM for inhibition of $\alpha_4\beta_1$ -mediated cell adhesion) with more than 500-fold selectivity over $\alpha_4\beta_7$, $\alpha_1\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_L\beta_2$ and gpIIb/IIIa receptors. Compound demonstrated tight-binding properties. Pretreatment of allergic sheep with a single nebulized dose (0.1 mg/kg) of compound significantly inhibited the early response and completely blocked the late airways response following antigen challenge, and it also prevented the development of airways hyperresponsiveness to carbachol. Potentially useful for the treatment of inflammatory diseases, especially bronchial asthma.

SOURCE – Biogen.

REFERENCES

1. Lin, K.-C. et al. (Biogen, Inc.) *Cell adhesion inhibitor*. EP 842196, WO 9703094.
2. Zheng, Z. et al. (Biogen, Inc.) *Cell adhesion inhibitors*. WO 9804247, WO 9804913.
3. Lin, K.-C. et al. *Selective, tight-binding inhibitors of integrin $\alpha_4\beta_1$ that inhibit allergic airway responses*. J Med Chem 1999, 42(5): 920.

NA-00226B

275592

ACTION – Compound isolated from *Streptomyces* sp. NA00226 (FERM-P-16196) that possesses cAMP-phosphodiesterase-inhibitory activity (IC_{50} = 5.3 μ M against enzyme from bovine tracheal smooth muscle). Another compound isolated from the same source is:

NA-00226C [275593]

SOURCE – Nippon Kayaku.

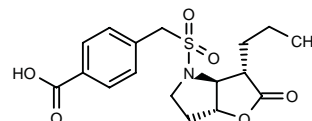
REFERENCES

1. Nishikiori, T. et al. (Nippon Kayaku Co., Ltd.) *Novel physiologically active substance NA00226B and C, their preparation method and their use*. JP 99060589.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

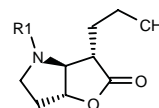
275317

4-[(3*S*,3*aS*,6*aR*)-2-Oxo-3-propylperhydrofuro[3,2-*b*]pyrrol-4-ylsulfonylmethyl]benzoic acid



C17 H21 N O6 S; Mol wt: 367.4199

ACTION – Nonpeptide inhibitor of serine proteases with selectivity for human neutrophil elastase (IC_{50} = 0.018 μ M) and cathepsin G (IC_{50} = 0.053 μ M) relative to other proteases such as trypsin (IC_{50} = 100 μ M), plasmin (IC_{50} = 10 μ M) and chymotrypsin (IC_{50} = 0.22 μ M), and thus expected to be particularly useful in the treatment of emphysema, chronic bronchitis and adult respiratory distress syndrome (ARDS). A representative compound from a series of hexahydrofuro[3,2-*b*]pyrrol-2-one derivatives, wherein the following are also included:



Compound	R1	Formula
275318	3-CO2H-PhSO2	C ₁₆ H ₁₉ NO ₆ S
275319	3-(PhCH2OCO)-PhCH2SO2	C ₂₄ H ₂₇ NO ₆ S
275320	2-indolyl-CO	C ₁₈ H ₂₀ N ₂ O ₃

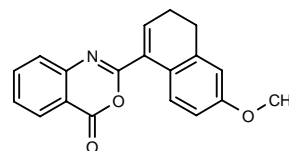
SOURCE – Glaxo Wellcome.

REFERENCES

1. Coote, S.J. et al. (Glaxo Group Ltd.) *Europyrrrolidine derivs. and their use as serine protease inhibitors*. WO 9912936.

276075

2-(6-Methoxy-3,4-dihydro-1-naphthyl)-4*H*-3,1-benzoxazin-4-one



C19 H15 N O3; Mol wt: 305.3315

ACTION – Potent inhibitor of human leukocyte elastase (HLE; IC_{50} = 0.61 μ M) proven to inhibit HLE-induced lung hemorrhage in mice by 31 and 55%, respectively, at doses of 10 and 30 mg/kg p.o. Potentially useful for the treatment of HLE-related diseases such as emphysema, acute respiratory distress syndrome, atherosclerosis and rheumatoid arthritis.

SOURCE – Dompé.

REFERENCES

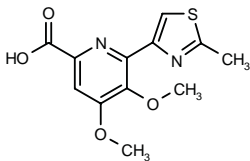
1. Arcadi, A. et al. *Synthesis and in vitro and in vivo evaluation of the 2-(6-methoxy-3',4'-dihydro-1'-naphtyl)-4H-3,1-benzoxazin-4-one as a new potent substrate inhibitor of human leukocyte elastase.* Bioorg Med Chem Lett 1999, 9(9): 1291.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

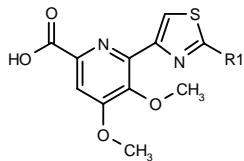
275333

4,5-Dimethoxy-6-(2-methylthiazol-4-yl)pyridine-2-carboxylic acid



C12 H12 N2 O4 S; Mol wt: 280.3028

ACTION – Agent for the treatment or prevention of hypertension, myocardial infarction, pulmonary hypertension, acute and chronic renal failure, cerebral ischemia, cirrhosis, septic shock, subarachnoid hemorrhage, asthma, atherosclerosis, cancer and diabetes, an inhibitor of endothelin-converting enzyme (ECE; IC₅₀ = 1.9 μM in CHO cells stably transfected with human ECE-1). Other specifically claimed compounds from this series of biaryl derivatives include the following:



Compound	R1	Formula
275334	C7H15	C ₁₈ H ₂₄ N ₂ O ₄ S
275335	NH2	C ₁₁ H ₁₁ N ₃ O ₄ S
275336	NHMe	C ₁₂ H ₁₃ N ₃ O ₄ S
275337	H	C ₁₁ H ₁₀ N ₂ O ₄ S

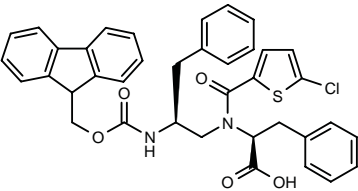
SOURCE – Warner-Lambert.

REFERENCES

1. Cheng, X.-M. et al. (Warner-Lambert Co.) *Small molecule biaryl cpds. as inhibitors of endothelin converting enzyme.* US 5891892.

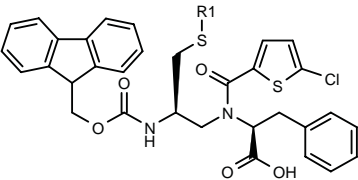
275991

N-(5-Chlorothien-2-ylcarbonyl)-N-[2(S)-(9H-fluoren-9-ylmethoxycarboxamido)-3-phenylpropyl]-L-phenylalanine



C38 H33 Cl N2 O5 S; Mol wt: 665.2067

ACTION – Endothelin-converting enzyme (ECE) inhibitor with selectivity over other proteases such as neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE), giving respective IC₅₀ values of 2, > 100 and > 100 μM. Potentially useful for the treatment of hypertension, myocardial infarction, pulmonary hypertension, heart failure, angina pectoris, renal failure, cerebral vasospasm, cerebral ischemia, migraine, asthma, atherosclerosis and cancer. Other exemplified compounds include the following:



Compound	R1	Formula
275994	t-BuS	C ₃₆ H ₃₇ ClN ₂ O ₅ S ₃
275997	H	C ₃₂ H ₂₉ ClN ₂ O ₅ S ₂

SOURCE – BASF.

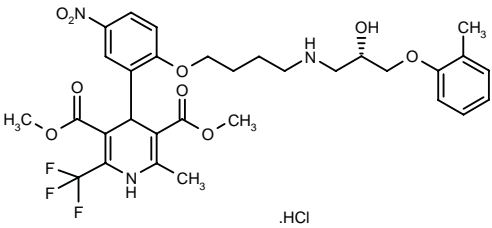
REFERENCES

1. Puhl, M. et al. (BASF AG) *Novel pharmaceutically active cpds., their preparation and use as ECE-inhibitors.* WO 9919320.

FR-172516

275394

4-[2-[4-[2(S)-Hydroxy-3-(2-methylphenoxy)-propylamino]butoxy]-5-nitrophenyl]-2-methyl-6-(trifluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester hydrochloride



C31 H36 F3 N3 O9 . HCl; Mol wt: 688.0923

SOURCE – Dompé.

REFERENCES

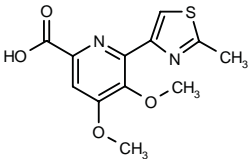
1. Arcadi, A. et al. *Synthesis and in vitro and in vivo evaluation of the 2-(6-methoxy-3',4'-dihydro-1'-naphthyl)-4H-3,1-benzoxazin-4-one as a new potent substrate inhibitor of human leukocyte elastase*. Bioorg Med Chem Lett 1999, 9(9): 1291.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

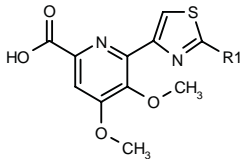
275333

4,5-Dimethoxy-6-(2-methylthiazol-4-yl)pyridine-2-carboxylic acid



C12 H12 N2 O4 S; Mol wt: 280.3028

ACTION – Agent for the treatment or prevention of hypertension, myocardial infarction, pulmonary hypertension, acute and chronic renal failure, cerebral ischemia, cirrhosis, septic shock, subarachnoid hemorrhage, asthma, atherosclerosis, cancer and diabetes, an inhibitor of endothelin-converting enzyme (ECE; IC₅₀ = 1.9 μM in CHO cells stably transfected with human ECE-1). Other specifically claimed compounds from this series of biaryl derivatives include the following:



Compound	R1	Formula
275334	C7H15	C ₁₈ H ₂₄ N ₂ O ₄ S
275335	NH2	C ₁₁ H ₁₁ N ₃ O ₄ S
275336	NHMe	C ₁₂ H ₁₃ N ₃ O ₄ S
275337	H	C ₁₁ H ₁₀ N ₂ O ₄ S

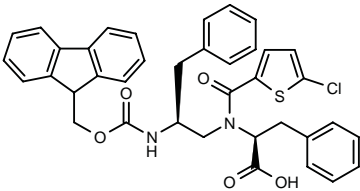
SOURCE – Warner-Lambert.

REFERENCES

1. Cheng, X.-M. et al. (Warner-Lambert Co.) *Small molecule biaryl cpds. as inhibitors of endothelin converting enzyme*. US 5891892.

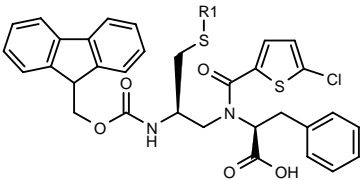
275991

N-(5-Chlorothien-2-ylcarbonyl)-N-[2(S)-(9H-fluoren-9-ylmethoxycarboxamido)-3-phenylpropyl]-L-phenylalanine



C38 H33 Cl N2 O5 S; Mol wt: 665.2067

ACTION – Endothelin-converting enzyme (ECE) inhibitor with selectivity over other proteases such as neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE), giving respective IC₅₀ values of 2, > 100 and > 100 μM. Potentially useful for the treatment of hypertension, myocardial infarction, pulmonary hypertension, heart failure, angina pectoris, renal failure, cerebral vasospasm, cerebral ischemia, migraine, asthma, atherosclerosis and cancer. Other exemplified compounds include the following:



Compound	R1	Formula
275994	t-BuS	C ₃₆ H ₃₇ ClN ₂ O ₅ S ₃
275997	H	C ₃₂ H ₂₉ ClN ₂ O ₅ S ₂

SOURCE – BASF.

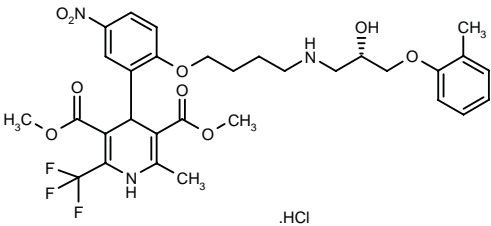
REFERENCES

1. Puhl, M. et al. (BASF AG) *Novel pharmaceutically active cpds., their preparation and use as ECE-inhibitors*. WO 9919320.

FR-172516

275394

4-[2-[4-[2(S)-Hydroxy-3-(2-methylphenoxy)-propylamino]butoxy]-5-nitrophenyl]-2-methyl-6-(trifluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester hydrochloride



C31 H36 F3 N3 O9 . HCl; Mol wt: 688.0923

ACTION – Dual calcium channel- and β -adrenoceptor-blocking agent (K_i = 29.3 and 44.1 nM, respectively), proven to relax K^+ -induced contractions in isolated aortic strips (ED_{50} = 5.5 nM), indicating blockade of voltage-dependent Ca^{2+} channels. *In vivo* in pithed rats, compound showed β -adrenoceptor-antagonist activity, antagonizing the increase in heart rate (HR) induced by isoproterenol with a pA_2 value of 6.55. In normotensive rats, compound (0.32-10 mg/kg i.v.) was more potent than amlodipine (a calcium channel blocker) in decreasing mean blood pressure (MBP) and HR, and in spontaneously hypertensive rats, both title compound and amlodipine induced potent and long-lasting (> 10 h) antihypertensive effects. In renal hypertensive dogs, FR-172516 administered once daily for 5 days at doses of 1-3.2 mg/kg p.o. decreased MBP without reflex tachycardia or increase in plasma renin activity. Potentially useful as an antihypertensive agent devoid of side effects evoked by activation of sympathetic tone.

SOURCES – Daicel; Fujisawa.

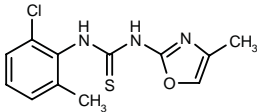
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TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES
AND ATHEROSCLEROSIS

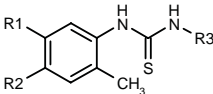
275190

N-(2-Chloro-6-methylphenyl)-*N'*-(4-methyloxazol-2-yl)thiourea



C12 H12 Cl N3 O S; Mol wt: 281.7658

ACTION – Antiatherosclerotic agent tested *in vivo* for its ability to increase HDL cholesterol levels (193% increase at a dose of 100 mg/kg/day for 8 days p.o. in rats fed a cholesterol-enriched diet). Also claimed for use in the treatment of dyslipoproteinemia and cardiovascular diseases. Within this series of specifically claimed substituted 1-aryl-3-heteroaryl-thiourea and substituted 1-aryl-3-heteroaryl-isothiurea derivatives, the following are also included:



Compound	R1	R2	R3	Formula
275191	Cl	H	4-Me-2-oxazolyl	C ₁₂ H ₁₂ ClN ₃ OS
275192	Cl	H	1,3,5-(Me)3-4-pyrazolyl	C ₁₄ H ₁₇ ClN ₄ S
275193	Cl	H	3-Me-5-isothiazolyl	C ₁₂ H ₁₂ ClN ₃ S ₂
275194	H	Cl	1,3,5-(Me)3-4-pyrazolyl	C ₁₄ H ₁₇ ClN ₄ S
275195	H	Cl	4-Me-2-oxazolyl	C ₁₂ H ₁₂ ClN ₃ OS

SOURCE – American Home Products.

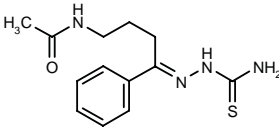
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275530

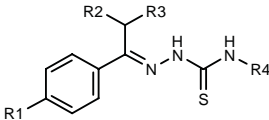
N-[4-[2-(Aminocarbothioyl)hydrazono]-4-phenylbutyl]-acetamide

N-[4-Phenyl-4-(thiosemicarbazono)butyl]acetamide



C13 H18 N4 O S; Mol wt: 278.3782

ACTION – Antiatherosclerotic agent that acts by increasing plasma levels of HDL cholesterol, as demonstrated *in vivo* in cholesterol-fed rats (81% increase at 33 mg/kg/day for 8 days orally). Other specifically claimed *N*-[4-[(aminothioxomethyl)hydrazono]-4-aryl-butyl]amides include the following:



Compound	R1	R2	R3	R4	Formula
275531	H	H	CH2CH2N(i-Pr)Ac	H	C ₁₆ H ₂₄ N ₄ OS
275532	H	H	CH2CH2N(i-Pr)COPh	H	C ₂₁ H ₂₆ N ₄ OS
275533	H	H	cyclohexyl-CON(i-Pr)CH2CH2	H	C ₂₁ H ₃₂ N ₄ OS
275534	H	H	cyclohexyl-CONHCH2CH2	H	C ₁₈ H ₂₆ N ₄ OS
275535	H	H	CH2CH2NHCOC5H11	H	C ₁₇ H ₂₆ N ₄ OS
275536	H	H	(CH2)2NHCOPh	Me	C ₁₉ H ₂₂ N ₄ OS
275537	H	Et	NHCOCH2Ph	H	C ₁₉ H ₂₂ N ₄ OS
275538	F	H	CH2CH2N(i-Pr)Ac	H	C ₁₆ H ₂₃ FN ₄ OS

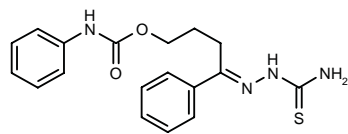
SOURCE – American Home Products.

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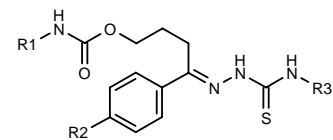
275539

N-Phenylcarbamic acid 4-phenyl-4-(thiosemicarbazono)-butyl ester



C18 H20 N4 O2 S; Mol wt: 356.4480

ACTION – Agent for the treatment of atherosclerosis that acts by increasing HDL cholesterol levels, as demonstrated in cholesterol-fed rats in which it produced a 150% increase in HDL levels at 100 mg/kg p.o. Other specifically claimed compounds from this series of 4-[(aminothioxomethyl)hydrazono]-4-arylbutyl carbamates include the following:



Compound	R1	R2	R3	Formula
275540	Bu	H	H	C ₁₆ H ₂₄ N ₄ O ₂ S
275541	cyclohexyl	H	H	C ₁₈ H ₂₆ N ₄ O ₂ S
275542	CH2Ph	H	H	C ₁₉ H ₂₂ N ₄ O ₂ S
275543	i-Pr	H	H	C ₁₅ H ₂₂ N ₄ O ₂ S
275544	Ph	H	Me	C ₁₉ H ₂₂ N ₄ O ₂ S
275545	1-Naph	H	H	C ₂₂ H ₂₂ N ₄ O ₂ S
275546	2-Ph-Ph	H	H	C ₂₄ H ₂₄ N ₄ O ₂ S
275547	Ph	Me	H	C ₁₉ H ₂₂ N ₄ O ₂ S
275549	3,4-(Cl)2-Ph	H	H	C ₁₈ H ₁₆ Cl ₂ N ₄ O ₂ S

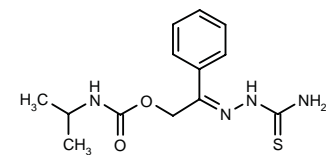
SOURCE – American Home Products.

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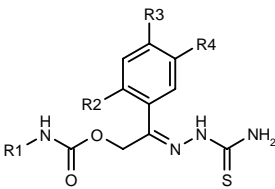
275553

N-Isopropylcarbamic acid 2-phenyl-2-(thiosemicarbazono)ethyl ester



C13 H18 N4 O2 S; Mol wt: 294.3772

ACTION – Agent for the treatment of atherosclerosis that acts by increasing HDL cholesterol levels, as demonstrated in cholesterol-fed rats in which it produced a 173.2% increase in HDL levels at 50 mg/kg p.o. A representative compound from a series of 2-[(aminothioxomethyl)hydrazono]-2-arylethyl carbamates, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
275554	Ph	H	H	H	C ₁₈ H ₁₈ N ₄ O ₂ S
275555	CH2Ph	H	H	H	C ₁₇ H ₁₈ N ₄ O ₂ S
275557	i-Pr	H	Cl	H	C ₁₃ H ₁₇ ClN ₄ O ₂ S
275558	i-Pr	H	OPh	H	C ₁₉ H ₂₂ N ₄ O ₃ S
275559	i-Pr	H	Ph	H	C ₁₉ H ₂₂ N ₄ O ₂ S
275560	i-Pr	H	F	H	C ₁₃ H ₁₇ FN ₄ O ₂ S
275561	i-Pr	H	H	Br	C ₁₃ H ₁₇ BrN ₄ O ₂ S
275562	i-Pr	F	H	H	C ₁₃ H ₁₇ FN ₄ O ₂ S

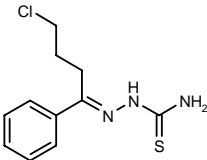
SOURCE – American Home Products.

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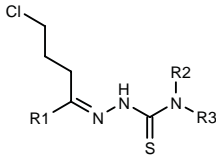
275563

1-(4-Chloro-1-phenylbutylidene)thiosemicarbazide



C11 H14 Cl N3 S; Mol wt: 255.7716

ACTION – Agent for the treatment of atherosclerosis that acts by increasing HDL cholesterol levels, as demonstrated in cholesterol-fed rats in which it produced a 204% increase in HDL levels at 100 mg/kg p.o. Other specifically claimed compounds from this series of 2-(4-chloro-1-arylbutylidene)hydrazinecarbothioamides include the following:



Compound	R1	R2	R3	Formula
275564	2-thienyl	H	H	C ₉ H ₁₂ ClN ₃ S ₂
275565	4-Cl-Ph	H	H	C ₁₁ H ₁₃ Cl ₂ N ₃ S
275566	3-Pyr	Me	H	C ₁₁ H ₁₅ ClN ₃ S
275567	Ph	Me	Me	C ₁₃ H ₁₈ ClN ₃ S
275568	Ph	2-Pyr-CH2CH2	H	C ₁₈ H ₂₁ ClN ₄ S
275569	Ph	n-C6H13	H	C ₁₇ H ₂₆ ClN ₃ S
275571	4-Me-Ph	H	H	C ₁₂ H ₁₆ ClN ₃ S
275572	4-MeO-Ph	H	H	C ₁₂ H ₁₆ ClN ₃ OS
275573	4-OH-Ph	H	H	C ₁₁ H ₁₄ ClN ₃ OS

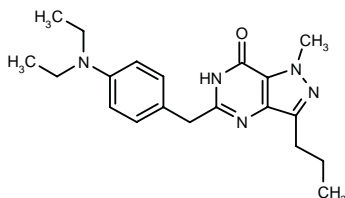
SOURCE – American Home Products.

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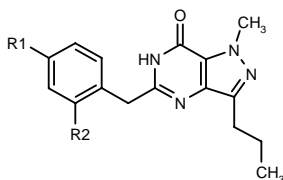
276236

5-[4-(Diethylamino)benzyl]-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one



C₂₀ H₂₇ N₅ O; Mol wt: 353.4673

ACTION – Potent and selective inhibitor of phosphodiesterase type 1 (PDE1), giving IC₅₀ values for PDE1, PDE2, PDE3, PDE4, PDE5 and PDE6 of 38 nM, 1.99 μM, 3.94 μM, 23 μM, 2.49 μM and 2.03 μM, respectively. Claimed for the treatment of hypertension, angina pectoris, congestive heart failure, myocardial infarction, restenosis, stroke, dementia, memory disturbances, atherosclerosis and incontinence, as well as male erectile dysfunction, premature labor, benign prostatic hyperplasia, asthma and glaucoma, among other disorders. Other compounds within this series of pyrazolo[4,3-d]pyrimidine derivatives include the following:



Compound	R1	R2	Formula
276238	H	NHSO ₂ Me	C ₁₇ H ₂₁ N ₅ O ₃ S
276240	NHSO ₂ Ph	H	C ₂₂ H ₂₃ N ₅ O ₃ S

SOURCE – Pfizer.

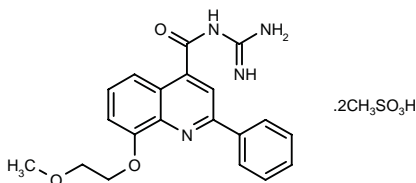
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MS-31-038^{1,2}

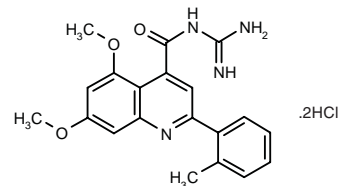
275395

N¹-[8-(2-Methoxyethoxy)-2-phenylquinolin-4-yl]-carbonylguanidine dimesylate



C₂₀ H₂₀ N₄ O₃ . 2 C H₄ O₃ S; Mol wt: 556.6142

ACTION – Na⁺/H⁺ exchange inhibitor shown to significantly reduce infarct size when administered at a dose of 10 mg/kg i.v. 1 min before the onset of reperfusion in a rat myocardial infarction model. Potentially useful for the treatment of ischemic heart disease. Another guanidine compound —**MS-31-050**— exhibits a different profile, exerting antiarrhythmic effects during ischemia in rats but being devoid of cardioprotective effect when given postischemia.



MS-31-050 [243184]:^{*1} C₂₀ H₂₀ N₄ O₃ . 2HCl

SOURCE – Mitsui Chemicals.

REFERENCES

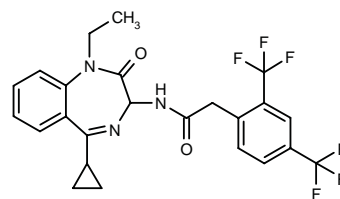
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*Identified compound **243184** (see **240726**) Drug Data Report 1997, 019(01): 0041.

ANTIARRHYTHMIC DRUGS

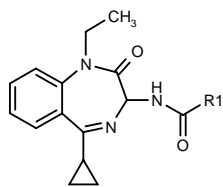
276345

2-[2,4-Bis(trifluoromethyl)phenyl]-N-(5-cyclopropyl-1-ethyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-acetamide



C₂₄ H₂₁ F₆ N₃ O₂; Mol wt: 497.4369

ACTION – Antiarrhythmic agent reported to be at least 10 times more potent in blocking K_{V(s)} channels than K_{V(r)} channels and with pharmacological properties of class III antiarrhythmic agents, i.e., prolongation of myocardial action potential *in vitro* without significant depression of the V_{max}¹ and prolongation of the Q-T_c interval in anesthetized dogs. It is therefore useful in the treatment or prevention of all types of arrhythmias, especially for controlling reentrant arrhythmias and for preventing sudden death due to ventricular fibrillation. Other specifically claimed benzodiazepine derivatives include the following:



Compound	R1	Formula
276348	3,5-(CF3)2-PhCH2	C ₂₄ H ₂₁ F ₆ N ₃ O ₂
276349	2-CF3-PhCH2	C ₂₃ H ₂₂ F ₃ N ₃ O ₂
276350	3-CF3-PhCH2	C ₂₃ H ₂₂ F ₃ N ₃ O ₂
276351	4-CF3-PhCH2	C ₂₃ H ₂₂ F ₃ N ₃ O ₂
276352	2,4-(CF3)2-Ph	C ₂₃ H ₁₉ F ₆ N ₃ O ₂
276353	3,5-(CF3)2-Ph	C ₂₃ H ₁₉ F ₆ N ₃ O ₂
276354	2,4-(Cl)2-Ph	C ₂₁ H ₁₉ Cl ₂ N ₃ O ₂
276355	3,4-(Cl)2-Ph	C ₂₁ H ₁₉ Cl ₂ N ₃ O ₂
276356	3,5-(Cl)2-Ph	C ₂₁ H ₁₉ Cl ₂ N ₃ O ₂
276357	3-CF3-4-Me-PhCH2	C ₂₄ H ₂₄ F ₃ N ₃ O ₂

SOURCE – Merck & Co.

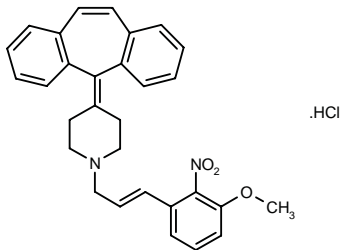
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AH-1058

261670

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-[3-(3-methoxy-2-nitrophenyl)-2(*E*)-propenyl]piperidine hydrochloride



C30 H28 N2 O3 . HCl; Mol wt: 501.0231

ACTION – Potent antiarrhythmic agent proven to inhibit (0.1-0.3 mg/kg i.v.) arrhythmias induced by ouabain and reperfusion, but not aconitine, in guinea pigs. Oral administration of compound (2-4 mg/kg) suppressed reperfusion-induced arrhythmias in rats more potently than verapamil. Compound potently suppressed L-type Ca²⁺ currents in isolated guinea pig cardiomyocytes.

SOURCE – Ajinomoto.

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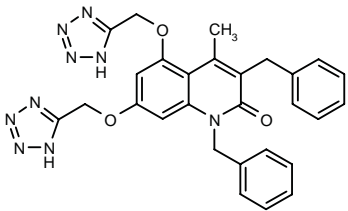
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6. Yoshimoto, R. et al. *Effects of a novel antiarrhythmic agent AH-1058 in experimental arrhythmia models*. Jpn J Pharmacol 1998, 76(Suppl.1): Abst P-571.

HEART FAILURE THERAPY

275705

1,3-Dibenzyl-4-methyl-5,7-bis(1*H*-tetrazol-5-ylmethoxy)-quinolin-2(1*H*)-one



C28 H25 N9 O3; Mol wt: 535.5655

ACTION – Agent for the treatment of heart failure and stunned myocardium with phospholamban-inhibitory properties, whose activity was demonstrated by an increase in calcium uptake into SR vesicles from guinea pig ventricular myocardium (18% increase at 10 μM), but not into the SR vesicles from fast skeletal muscle. Compound increased left ventricular pressure in guinea pig hearts with an EC₅₀ value of 2 μM. It completely inhibited the development of stunned myocardium in isolated perfused guinea pig hearts at 10 μM.

SOURCE – Orion Corporation.

REFERENCES

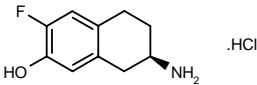
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TREATMENT OF SHOCK

ST-1238

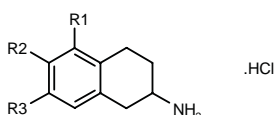
275670

7(*R*)-Amino-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ol hydrochloride



C10 H12 F N O . HCl; Mol wt: 217.6697

ACTION – Agent for the treatment of septic shock, inflammatory and/or autoimmune diseases that acts by inhibiting cytokine production. Compound protected from lethality induced by *Escherichia coli* lipopolysaccharide (LPS) in mice sensitized with D-galactosamine (60% increase in survival at 18 mg/kg i.v. pre/postchallenge treatment; 44% increase in survival at this dose given postchallenge). Similar effects were observed when using *Staphylococcus aureus* as inducer of lethal effects in sensitized mice. Compound reduced tumor necrosis factor (TNF) production (39%) in rat blood stimulated with LPS, as well as the production of other proinflammatory cytokines (IL-1 β and IL-6) elicited by enterotoxin SEB in sensitized mice. Other specifically claimed 2-amino-tetraline derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
ST-1237 [275671]	H	F	OH	S	C ₁₀ H ₁₂ FNO.HCl
ST-1269 [275672]	F	F	OMe	racemic	C ₁₁ H ₁₃ F ₂ NO.HCl
ST-1275 [275673]	H	F	Me	racemic	C ₁₁ H ₁₄ FN.HCl
ST-1267 [275674]	H	OH	F	racemic	C ₁₀ H ₁₂ FNO.HCl
ST-1274 [275675]	H	Me	Ac	racemic	C ₁₃ H ₁₇ NO.HCl
ST-1262 [275676]	H	OMe	F	racemic	C ₁₁ H ₁₄ FNO.HCl

SOURCE – Sigma-Tau.

REFERENCES

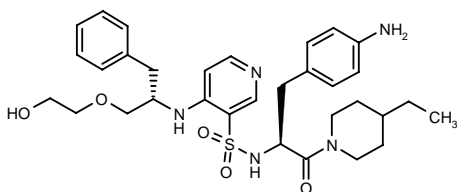
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

273697

N-[1(*S*)-(4-Aminobenzyl)-2-(4-ethyl-1-piperidinyl)-2-oxo-ethyl]-4-[1(*S*)-benzyl-2-(2-hydroxyethoxy)ethylamino]-pyridine-3-sulfonamide



C32 H43 N5 O5 S; Mol wt: 609.7877

ACTION – Anticoagulant that acts by inhibiting thrombin (K_i = 147 nM against human enzyme) and displays good selectivity over other serine proteases such as trypsin, chymotrypsin, plasmin, kallikrein and factor Xa. At a concentration of 5 μ M it doubled the human plasma

activated partial thromboplastin time (aPTT). In rat, compound exhibited good oral bioavailability (55%) and showed strong (complete inhibition at 30 mg/kg p.o.) and long-lasting (4 h) inhibition of thrombus formation in an *in vivo* rat model of venous thrombosis. It is devoid of significant effects on the complement cascade *in vitro*.

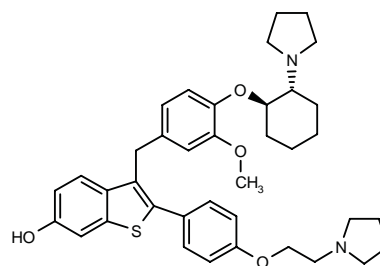
SOURCE – Novartis.

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273702

trans-3-[3-Methoxy-4-[2-(1-pyrrolidinyl)cyclohexyloxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzothiophen-6-ol



C38 H46 N2 O4 S; Mol wt: 626.8574

ACTION – Site-directed thrombin inhibitor with high selectivity over other serine proteases such as trypsin and other coagulation factors such as factor Xa. In the rat arteriovenous shunt model, compound was able to reduce clot size.

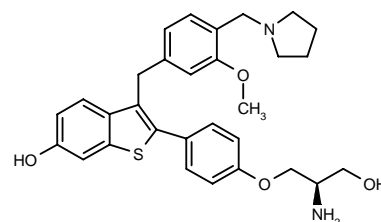
SOURCE – Lilly.

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2. Takeuchi, K. et al. *Dibasic benzo[b]thiophene derivatives as a novel class of active site directed thrombin inhibitors: 4. SAR studies on the conformationally restricted C3-side chain of hydroxybenzo[b]thiophenes*. Bioorg Med Chem Lett 1999, 9(5): 759.

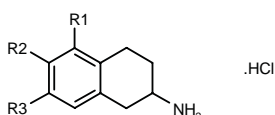
273707

2-[4-[2(*R*)-Amino-3-hydroxypropoxy]phenyl]-3-[3-methoxy-4-(1-pyrrolidinylmethyl)benzyl]benzothiophen-6-ol



C30 H34 N2 O4 S; Mol wt: 518.6746

ACTION – Agent for the treatment of septic shock, inflammatory and/or autoimmune diseases that acts by inhibiting cytokine production. Compound protected from lethality induced by *Escherichia coli* lipopolysaccharide (LPS) in mice sensitized with D-galactosamine (60% increase in survival at 18 mg/kg i.v. pre/postchallenge treatment; 44% increase in survival at this dose given postchallenge). Similar effects were observed when using *Staphylococcus aureus* as inducer of lethal effects in sensitized mice. Compound reduced tumor necrosis factor (TNF) production (39%) in rat blood stimulated with LPS, as well as the production of other proinflammatory cytokines (IL-1 β and IL-6) elicited by enterotoxin SEB in sensitized mice. Other specifically claimed 2-amino-tetraline derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
ST-1237 [275671]	H	F	OH	S	C ₁₀ H ₁₂ FNO.HCl
ST-1269 [275672]	F	F	OMe	racemic	C ₁₁ H ₁₃ F ₂ NO.HCl
ST-1275 [275673]	H	F	Me	racemic	C ₁₁ H ₁₄ FN.HCl
ST-1267 [275674]	H	OH	F	racemic	C ₁₀ H ₁₂ FNO.HCl
ST-1274 [275675]	H	Me	Ac	racemic	C ₁₃ H ₁₇ NO.HCl
ST-1262 [275676]	H	OMe	F	racemic	C ₁₁ H ₁₄ FNO.HCl

SOURCE – Sigma-Tau.

REFERENCES

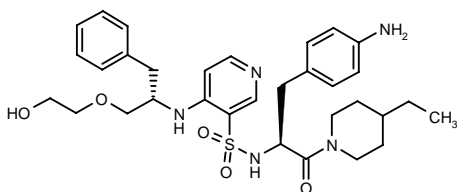
1. Fanto, N. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *2-Aminotetralines, a process for their preparation, and pharmaceutical compsns., for the prevention and therapeutic treatment of inflammatory and/or autoimmune pathologies*. WO 9915494.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

273697

N-[1(*S*)-(4-Aminobenzyl)-2-(4-ethyl-1-piperidinyl)-2-oxoethyl]-4-[1(*S*)-benzyl-2-(2-hydroxyethoxy)ethylamino]-pyridine-3-sulfonamide



C32 H43 N5 O5 S; Mol wt: 609.7877

ACTION – Anticoagulant that acts by inhibiting thrombin (K_i = 147 nM against human enzyme) and displays good selectivity over other serine proteases such as trypsin, chymotrypsin, plasmin, kallikrein and factor Xa. At a concentration of 5 μ M it doubled the human plasma

activated partial thromboplastin time (aPTT). In rat, compound exhibited good oral bioavailability (55%) and showed strong (complete inhibition at 30 mg/kg p.o.) and long-lasting (4 h) inhibition of thrombus formation in an *in vivo* rat model of venous thrombosis. It is devoid of significant effects on the complement cascade *in vitro*.

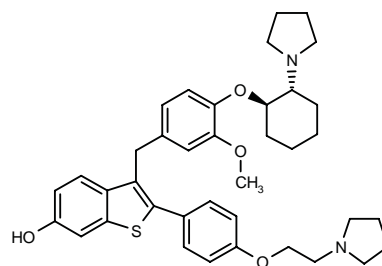
SOURCE – Novartis.

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1. Brundish, D.E. et al. (Ciba-Geigy AG) *Thrombin inhibitors*. WO 9746553.
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273702

trans-3-[3-Methoxy-4-[2-(1-pyrrolidinyl)cyclohexyloxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzothiophen-6-ol



C38 H46 N2 O4 S; Mol wt: 626.8574

ACTION – Site-directed thrombin inhibitor with high selectivity over other serine proteases such as trypsin and other coagulation factors such as factor Xa. In the rat arteriovenous shunt model, compound was able to reduce clot size.

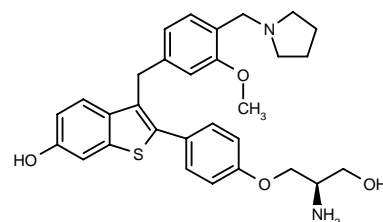
SOURCE – Lilly.

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2. Takeuchi, K. et al. *Dibasic benzo[b]thiophene derivatives as a novel class of active site directed thrombin inhibitors: 4. SAR studies on the conformationally restricted C3-side chain of hydroxybenzo[b]thiophenes*. Bioorg Med Chem Lett 1999, 9(5): 759.

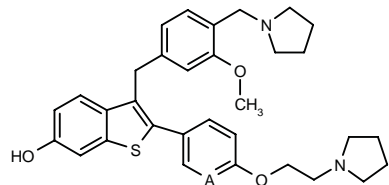
273707

2-[4-[2(*R*)-Amino-3-hydroxypropoxy]phenyl]-3-[3-methoxy-4-(1-pyrrolidinylmethyl)benzyl]benzothiophen-6-ol



C30 H34 N2 O4 S; Mol wt: 518.6746

ACTION – Potent active-site-directed thrombin inhibitor ($K_i = 0.4 \text{ nM}$) shown to prolong the thrombin time (TT), activated partial thromboplastin time (aPTT) and prothrombin time (PT) by 2-fold at concentrations of 0.039, 0.66 and 0.6 μM , respectively. *In vivo* in a rat arteriovenous shunt model of thrombosis, compound reduced clot weight with an ED_{50} of 2.3 mg/kg/h i.v. Other compounds from this series of dibasic benzo[*b*]thiophene derivatives include the following:



Compound	A	Formula
273705	CH	$\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_3\text{S}$
273706	N	$\text{C}_{32}\text{H}_{37}\text{N}_3\text{O}_3\text{S}$

SOURCE – Lilly.

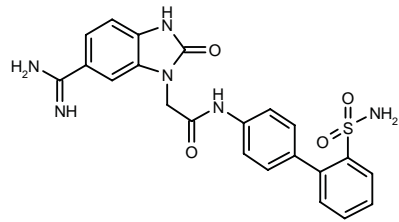
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2. Zhang, M. et al. *Dibasic benzo[*b*]thiophene derivatives as a novel class of active site directed thrombin inhibitors: 2. Sidechain optimization and demonstration of in vivo efficacy*. Bioorg Med Chem Lett 1999, 9(5): 775.

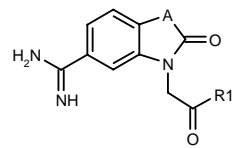
275228

2-(6-Amidino-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-*N*-(2'-sulfamoylbiphenyl-4-yl)acetamide

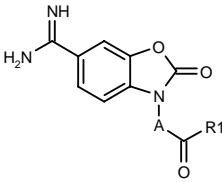


C22 H20 N6 O4 S; Mol wt: 464.5040

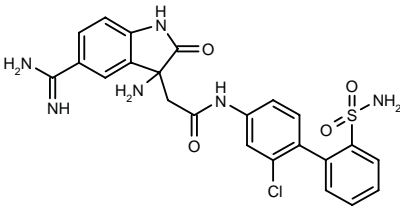
ACTION – Anticoagulant, an inhibitor of factor Xa exhibiting a K_i of $< 15 \text{ }\mu\text{M}$. Within this series of specifically claimed benzimidazolinone, benzoxazolinone, benzopiperazinone and indanone derivatives, the following are also included:



Compound	R1	A	Formula
275229	4-(4-Cl-Ph)-2-thiazolyl-NH	-NH-	$\text{C}_{19}\text{H}_{15}\text{ClN}_6\text{O}_2\text{S}$
275231	4-Ph-Ph	-NHCH2-	$\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$



Compound	R1	A	Formula
275230	4-(4-oxazolyl)-PhNH	-CH2-	$\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_4$
275232	4-Ph-Ph	-(CH2)2-	$\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_3$
275233	4-[2-(NH2SO2)-Ph]-2-Pyr-NH	-CH2-	$\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_5\text{S}$



275234: C23 H21 Cl N6 O4 S

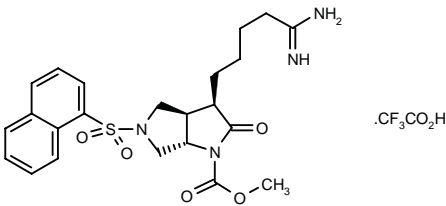
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Han, Q. et al. (DuPont Pharmaceuticals Co.) *Benzimidazolinones, benzoxazolinones, benzopiperazinones, indanones, and derivs. thereof as inhibitors of factor Xa*. WO 9912903.

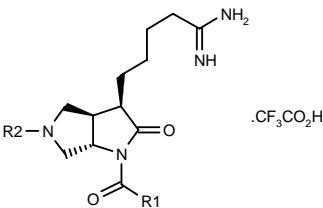
275321

(3*R*,3*aR*,6*aS*)-3-(4-Amidinobutyl)-5-(1-naphthalenylsulfonyl)-2-oxooctahydropyrrolo[3,4-*b*]pyrrole-1-carboxylic acid methyl ester trifluoroacetate



C23 H28 N4 O5 S . C2 H F3 O2; Mol wt: 586.5851

ACTION – Nonpeptide inhibitor of serine proteases with potent inhibitory activity against thrombin, trypsin, factor Xa, factor XIa, factor XIIa, tissue plasminogen activator (tPA) and factor VIIa ($\text{IC}_{50} = 0.004\text{-}0.537 \text{ }\mu\text{M}$). It is therefore expected to be particularly useful in the treatment of disorders of the vascular system related to the blood coagulation and/or fibrinolytic cascades, i.e., thrombosis. A representative compound from a series of pyrrolopyrrolidine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
275322	OMe	2-indolyl-CO	C ₂₂ H ₂₇ N ₅ O ₄ .C ₂ HF ₃ O ₂
275323	OMe	2-benzimidazolyl-SO2	C ₂₆ H ₂₆ N ₆ O ₅ S.C ₂ HF ₃ O ₂
275324	OMe	2-Naph-SO2	C ₂₃ H ₂₈ N ₄ O ₅ S.C ₂ HF ₃ O ₂
275325	NHMe	2-indolyl-CO	C ₂₂ H ₂₈ N ₆ O ₃ .C ₂ HF ₃ O ₂

Certain compounds of the invention exhibited potent and selective inhibition of human neutrophil elastase, and may thus be useful for the treatment of emphysema, chronic bronchitis and adult respiratory distress syndrome (ARDS).

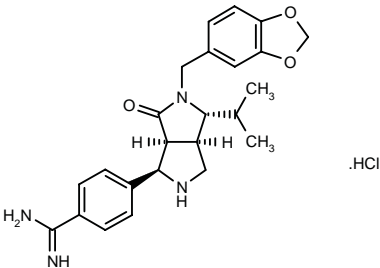
SOURCE – Glaxo Wellcome.

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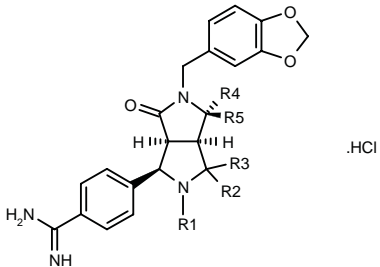
275345

4-[(1*R**,3*aR**,4*R**,6*aS**)-5-(1,3-Benzodioxol-5-ylmethyl)-4-isopropyl-6-oxooctahydropyrrolo[3,4-*c*]pyrrol-1-yl]benzamidinium hydrochloride



C₂₄ H₂₈ N₄ O₃ . HCl; Mol wt: 456.9711

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of thrombin (K_i = 0.005 μM) with much lower inhibitory activity against other serine proteases such as trypsin (K_i = 7.5 μM). Other specifically claimed oxopyrrolo-pyrrole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
275348	Me	Me	Me	Et	Et	C ₂₈ H ₃₂ N ₄ O ₃ .HCl
275349	Me	Me	Me	i-Pr	H	C ₂₇ H ₃₄ N ₄ O ₃ .HCl
275350	-(CH ₂) ₃ -	H	cyclopropyl	H	H	C ₂₇ H ₃₀ N ₄ O ₃ .HCl
275351	-(CH ₂) ₃ -	H	Et	H	H	C ₂₈ H ₃₀ N ₄ O ₃ .HCl

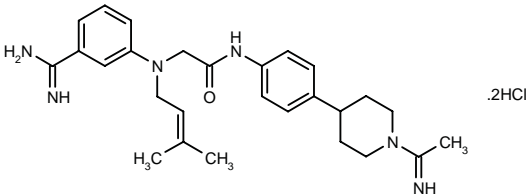
SOURCE – Roche.

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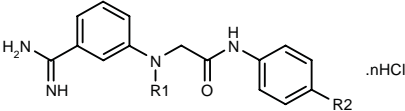
275410

2-[*N*-(3-Amidinophenyl)-*N*-(3-methyl-2-butenyl)amino]-*N*-[4-(1-iminoethyl-4-piperidiny)phenyl]acetamide dihydrochloride



C₂₇ H₃₆ N₆ O . 2HCl; Mol wt: 533.5442

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa (IC₅₀ = 4 nM; IC₅₀ thrombin = 15 μM). Compound exhibited anti-coagulant activity in human blood, doubling the plasma prothrombin time at a concentration of 0.091 μM. Other compounds from this series of 3-amidinoaniline derivatives include the following:



Compound	R1	R2	n	Formula
275411	CH ₂ CH=C(Me) ₂	i-PrO	1	C ₂₃ H ₃₀ N ₄ O ₂ .HCl
275412	3-OH-PhCH ₂	1-[NH=C(Me)]-4-Pip	2	C ₂₉ H ₃₄ N ₆ O ₂ .2HCl
275413	CH ₂ Ph	1-[NH=C(Me)]-4-Pip	2	C ₂₉ H ₃₄ N ₆ O ₂ .2HCl
275414	3-(CO ₂ HCH ₂ O)-PhCH ₂	1-[NH=C(Me)]-4-Pip	2	C ₃₁ H ₃₆ N ₆ O ₄ .2HCl
275415	1-Naph-CH ₂	1-[NH=C(Me)]-4-Pip	2	C ₃₃ H ₃₈ N ₆ O ₂ .HCl
275416	5-Me-4-imidazolyl-CH ₂	1-[NH=C(Me)]-4-Pip	2	C ₂₇ H ₃₄ N ₈ O ₂ .HCl
275417	H	1-[NH=C(Me)]-4-Pip-O	2	C ₂₂ H ₂₈ N ₆ O ₂ .2HCl

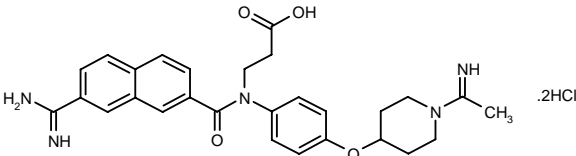
SOURCE – Kissei.

REFERENCES

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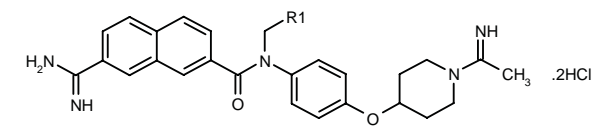
275488

N-(7-Amidino-2-naphthalenylcarbonyl)-*N*-[4-(1-iminoethyl-4-piperidinyloxy)phenyl]-β-alanine dihydrochloride



C₂₈ H₃₁ N₅ O₄ . 2HCl; Mol wt: 574.5057

ACTION – Anticoagulant and antithrombotic agent with factor Xa-inhibitory activity. In an *ex vivo* assay in mice, compound was shown to prolong prothrombin time (PT) by 2.9-fold compared to controls following i.v. administration. A representative compound from a series of naphthamide derivatives, wherein the following are also included:



Compound	R1	Formula
275489	CO2H	C ₂₇ H ₂₉ N ₅ O ₄ .2HCl
275491	CH2CH2CO2Et	C ₃₁ H ₃₇ N ₅ O ₄ .2HCl
275493	CH2CH2CO2H	C ₂₉ H ₃₃ N ₅ O ₄ .2HCl

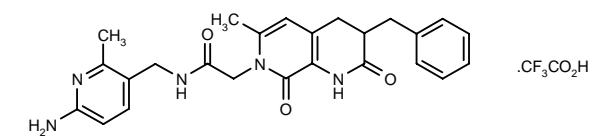
SOURCE – Yamanouchi.

REFERENCES

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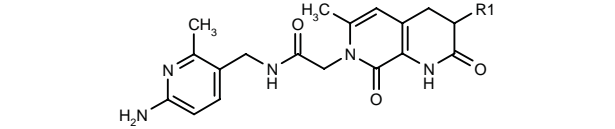
275595

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[3-benzyl-6-methyl-2,8-dioxo-1,2,3,4,7,8-hexahydro[1,7]naphthyridin-7-yl]acetamide trifluoroacetate



C25 H27 N5 O3 . C2 H F3 O2; Mol wt: 559.5422

ACTION – Antithrombotic agent, an inhibitor of human thrombin (K_i = 0.36 nM). Other specifically claimed fused lactam compounds include the following:



Compound	R1	Isomer	Formula
275596	H		C ₁₈ H ₂₁ N ₅ O ₃
275597	CH2Ph		C ₂₅ H ₂₇ N ₅ O ₃
275598	CH2Ph	S	C ₂₅ H ₂₇ N ₅ O ₃
275599	CH2Ph	R	C ₂₅ H ₂₇ N ₅ O ₃
275600	3-F-PhCH2		C ₂₅ H ₂₆ FN ₅ O ₃
275601	3,5-(F)2-PhCH2		C ₂₅ H ₂₅ F ₂ N ₅ O ₃
275602	2,5-(F)2-PhCH2		C ₂₅ H ₂₅ F ₂ N ₅ O ₃
275603	cyclobutyl-CH2		C ₂₃ H ₂₉ N ₅ O ₃
275604	(S)-CH2CH2CH(Me)Et		C ₂₄ H ₃₃ N ₅ O ₃

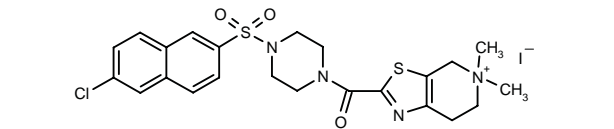
SOURCE – Merck & Co.

REFERENCES

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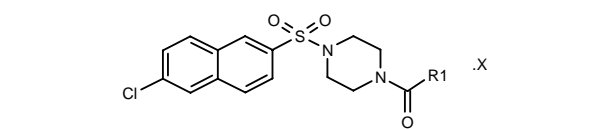
276399

2-[4-(6-Chloro-2-naphthylsulfonyl)-1-piperazinylcarbonyl]-5,5-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-5-ium iodide

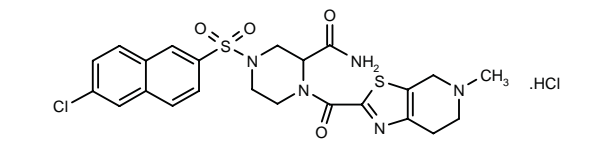


C23 H26 Cl I N4 O3 S2 ; Mol wt: 632.9684

ACTION – Anticoagulant with potent inhibitory activity against factor Xa. Compound is reported to have a fast onset and good duration of action and is effective following oral administration, while being associated with few side effects. Other representative sulfonyl compounds are:



Compound	R1	X	Formula
276400	4-(1-oxido-4-Pyr)-Ph		C ₂₆ H ₂₂ ClN ₃ O ₄ S
276401	4-(1-oxido-2-Pyr)-Ph		C ₂₆ H ₂₂ ClN ₃ O ₄ S
276403	5-Me-4,5,6,7-tetrahydrothiazolo[5,4- <i>c</i>]pyridin-2-yl	HCl	C ₂₂ H ₂₃ ClN ₄ O ₃ S ₂ .HCl
276404	5-oxido-5-Me-4,5,6,7-tetrahydrothiazolo[5,4- <i>c</i>]pyridin-2-yl		C ₂₂ H ₂₃ ClN ₄ O ₄ S ₂
276407	4-(4-Pyr)-3-cyclohexen-1-yl	HCl	C ₂₆ H ₂₆ ClN ₃ O ₃ S.HCl



276406: C23 H24 Cl N5 O4 S2 . HCl

SOURCE – Daiichi Pharmaceutical.

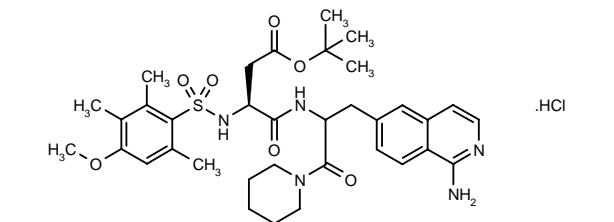
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ORG-37476*

270623

N-[1-(1-Amino-6-isoquinolinylmethyl)-2-oxo-2-(1-piperidinyl)ethyl]-3(*S*)-(4-methoxy-2,3,6-trimethylphenyl-sulfonamido)succinamic acid *tert*-butyl ester hydrochloride



C35 H47 N5 O7 S . HCl; Mol wt: 718.3112

ACTION – Anticoagulant, a potent thrombin inhibitor (IC_{50} = 0.082 μ M) with excellent selectivity over trypsin (IC_{50} = 378 μ M). In a model of *in vitro* intestinal absorption using Caco-2 cell monolayers, compound showed good permeability, suggesting good oral absorption *in vivo*.

SOURCE – Organon.

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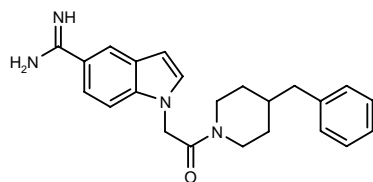
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*Identified compound **270623** Drug Data Report 1999, 021(01): 0041.

XU-817*

261716

1-[2-(4-Benzylpiperidin-1-yl)-2-oxoethyl]-1H-indole-5-carboxamide



C23 H26 N4 O; Mol wt: 374.4854

ACTION – Potent thrombin inhibitor (K_i = 18 nM) with more than 500-fold selectivity over trypsin and factor Xa (K_i > 15,000 and 10,300 nM, respectively); compared with DuP-714, XU-817 was 400-fold less potent but much more selective. Compound showed good antithrombotic efficacy *in vivo* in the rat vena cava thrombosis model, with an ED_{50} of 0.8 mg/kg/h i.v., only 20-fold higher than that of DuP-714.

SOURCE – DuPont Pharmaceuticals.

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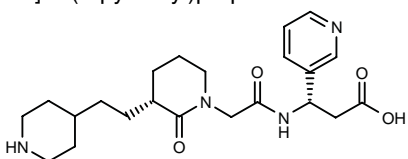
2. Dominguez, C. et al. *Design and synthesis of potent and selective 5,6-fused heterocyclic thrombin inhibitors*. Bioorg Med Chem Lett 1999, 9(7): 925.

*Identified compound **261716** (see **261201**) Drug Data Report 1998, 020(04): 0317.

ANTIPLATELET THERAPY

275224

3(S)-[2-[2-Oxo-3(R)-[2-(4-piperidinyl)ethyl]piperidin-1-yl]acetamido]-3-(3-pyridinyl)propionic acid



C22 H32 N4 O4; Mol wt: 416.5188

ACTION – Antiplatelet and antithrombotic agent, a fibrinogen (gpIIb/IIIa) receptor antagonist proven to inhibit ADP-induced platelet aggregation both *in vitro* and *ex vivo* in dogs following oral administration.

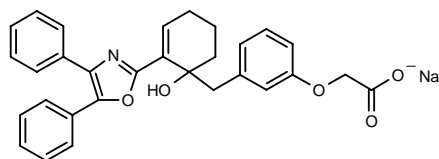
SOURCE – Merck & Co.

REFERENCES

1. Hutchinson, J.H. et al. (Merck & Co., Inc.) *Fibrinogen receptor antagonist*. US 5889023.

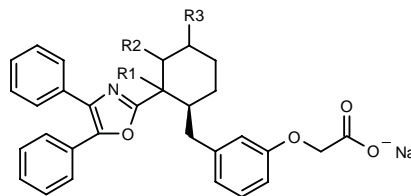
276455

2-[3-[2-(4,5-Diphenyloxazol-2-yl)-1-hydroxy-2-cyclohexen-1-ylmethyl]phenoxy]acetic acid sodium salt



C30 H26 N Na O5; Mol wt: 503.5274

ACTION – PGI_2 agonist shown to inhibit ADP-induced aggregation of human platelet-rich plasma by over 90% at a concentration of 0.10 μ M. Potentially useful in the treatment of arterial obstruction, restenosis following percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and cerebrovascular or ischemic heart disease. Other representative 4,5-diaryloxazole derivatives include the following:



Compound	R1	R2	R3	Formula
276457	bond		OH	$C_{30}H_{26}NNaO_5$
276458	-O-		H	$C_{30}H_{26}NNaO_5$

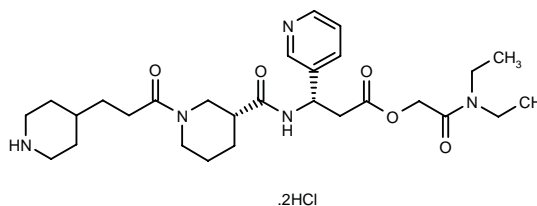
SOURCE – Fujisawa.

REFERENCES

1. Hattori, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *4,5-Diaryloxazole cpds*. WO 9921843.

276681

3(S)-[1-[3-(4-Piperidinyl)propionyl]piperidin-3(R)-ylcarboxamido]-3-(3-pyridinyl)propionic acid *N,N*-diethylcarbamoylmethyl ester dihydrochloride



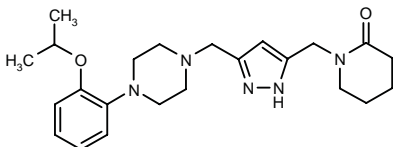
C28 H43 N5 O5 . 2HCl; Mol wt: 602.5995

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

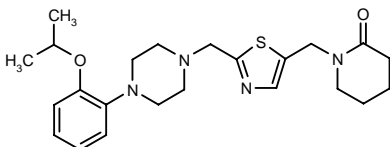
276083

1-[3-[4-(2-Isopropoxyphenyl)piperazin-1-ylmethyl]-1H-pyrazol-5-ylmethyl]piperidin-2-one



C23 H33 N5 O2: Mol wt: 411.5467

ACTION – Agent for the treatment of benign prostatic hyperplasia, an α_1 -adrenoceptor antagonist with selectivity for the α_{1a} subtype ($IC_{50} = 2.1$ nM) over α_{1b} ($IC_{50} = 3915$ nM) and α_{1d} ($IC_{50} = 177$ nM) subtypes. In a functional assay, it exhibited IC_{50} values of 1.3 and 31.9 μ M, respectively, for inhibition of norepinephrine-induced contractions in rat prostate and rat aorta, thus showing selectivity for prostatic over aortic tissue. *In vivo*, compound was found to inhibit the phenylephrine-induced increase in intraurethral pressure in dogs at 10 μ g/kg i.v., while showing little effect on mean arterial pressure. Another compound from this series of specifically claimed aryl-substituted piperazines is:



276084: C23 H32 N4 O2 S

SOURCE – Ortho-McNeil.

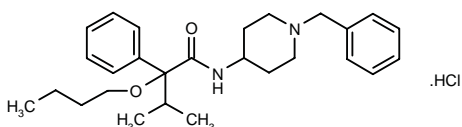
REFERENCES

1. Hutchings, R.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Heterocycles useful in the treatment of benign prostatic hyperplasia and intermediates thereof*. WO 9919299.

TREATMENT OF URINARY INCONTINENCE

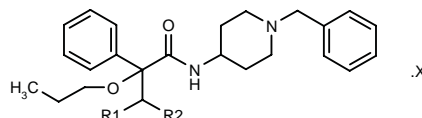
276268

N-(1-Benzyl-4-piperidinyl)-2-butoxy-3-methyl-2-phenylbutyramide hydrochloride



C27 H38 N2 O2 . HCl; Mol wt: 459.0701

ACTION – Anticholinergic agent and calcium antagonist with high selectivity for the bladder as compared to salivary glands, potentially useful in the treatment or prevention of urinary disorders such as pollakiuria or urinary incontinence. Compound displayed comparable potency to oxybutynin and propiverine for inhibition of acetylcholine-induced rat bladder contractions (ID_{50} = 9.8 mg/kg i.d. vs. 3.4 mg/kg i.d. for oxybutynin and 9.9 mg/kg i.d. for propiverine), while showing less potent inhibition of salivation in rats (ID_{50} = 56.6 mg/kg p.o. vs. 3.5 mg/kg p.o. for oxybutynin and 9.2 mg/kg p.o. for propiverine). Other exemplified arylacetic amide derivatives are:



Compound	R1	R2	X	Formula
276269	Me	Me	HCl	C ₂₈ H ₃₆ N ₂ O ₂ ·HCl
276270	-CH ₂ CH ₂ -		fumarate	C ₂₆ H ₃₄ N ₂ O ₂ ·C ₄ H ₄ O ₄

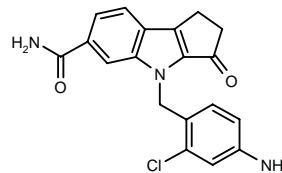
SOURCE – SS Pharmaceutical.

REFERENCES

1. Kaihoh, T. et al. (SS Pharmaceutical, Ltd.) *Arylacetic amide deriv. or salt thereof, and pharmaceutical comprising it.* EP 913393.

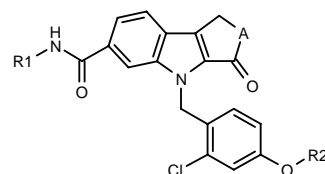
276518

4-(4-Amino-2-chlorobenzyl)-3-oxo-1,2,3,4-tetrahydro-
cyclopenta[*b*]indole-6-carboxamide



C19 H16 Cl N3 O2; Mol wt: 353.8074

ACTION – cGMP-phosphodiesterase (cGMP-PDE) inhibitor ($IC_{50} < 100$ nM for inhibition of cGMP-PDE from human platelets) with advantages over prior art compounds such as stronger activity, more suitable half-life or reduced side effects. Potentially useful in the treatment of hypertension, angina pectoris, micturition disorders, incontinence and urine storage disorders. Other exemplified tricyclic compounds are:



Compound	R1	R2	A	Formula
276519	2-thienyl-CH2	Me	-CH2-	C ₂₄ H ₁₉ ClN ₂ O ₃ S
276520	Pr	Me	-CH2-	C ₂₃ H ₂₃ ClN ₂ O ₃
276521	3-Pyr-CH2	H	-(CH2)2-	C ₂₈ H ₂₂ ClN ₂ O ₃
276522	2-furyl-CH2	Me	-(CH2)2-	C ₂₈ H ₂₃ ClN ₂ O ₄

SOURCE – Fujisawa.

REFERENCES

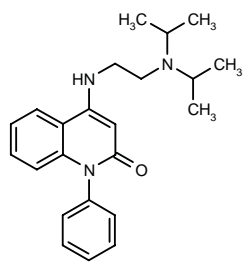
1. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Tricyclic cpds. as cGMP-PDE inhibitors*. WO 9921831.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

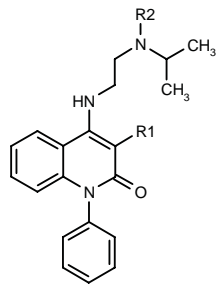
275468

4-[2-(Diisopropylamino)ethylamino]-1-phenyl-2(1*H*)-quinolinone



C23 H29 N3 O; Mol wt: 363.5021

ACTION – Antiulcer agent proven to inhibit water immersion-restraint stress-induced ulcers in rats by 97.7% at a dose of 100 mg/kg p.o. Within this series of substituted quinolone derivatives, the following are also included:



Compound	R1	R2	Formula
275469	CO2Et	i-Pr	C ₂₆ H ₃₃ N ₃ O ₃
275470	CO2Et	CH2CH2N(Et)2	C ₂₉ H ₄₀ N ₄ O ₃
275471	CN	i-Pr	C ₂₄ H ₂₈ N ₄ O
275473	CO2H	i-Pr	C ₂₄ H ₂₉ N ₃ O ₃

SOURCE – SS Pharmaceutical.

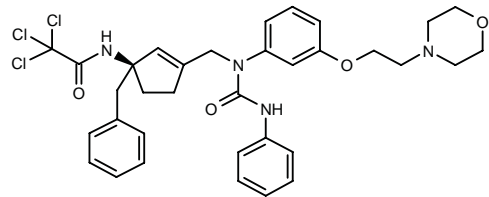
REFERENCES

1. Sata, Y. et al. (SS Pharmaceutical, Ltd.) *Substituted quinolone derivs. and medicines containing them*. JP 99071351.

IRRITABLE BOWEL SYNDROME THERAPY

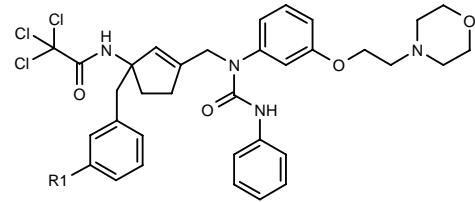
276499

N-[1(*S*)-Benzyl-3-[*N*-[3-[2-(4-morpholinyl)ethoxy]phenyl]-*N'*-phenylureidomethyl]-2-cyclopenten-1-yl]-2,2,2-trichloroacetamide



C34 H37 Cl3 N4 O4; Mol wt: 672.0493

ACTION – Motilin receptor antagonist that competes with erythromycin for the motilin receptor *in vitro* and suppresses smooth muscle contractions induced by motilin and erythromycin, with activity and potency comparable to OHM-11526 *in vitro*. It is expected to be particularly useful in the treatment of irritable bowel syndrome and esophageal reflux. Other specifically claimed cyclopentene derivatives are:



Compound	R1	Isomer	Formula
276500	H	R	C ₃₄ H ₃₇ Cl ₃ N ₄ O ₄
276501	Cl	S	C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄
276502	Cl		C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄
276503	Cl	R	C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄

SOURCE – Ortho-McNeil.

REFERENCES

1. Chen, R.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Cyclopentene derivs. useful as antagonists of the motilin receptor*. WO 9921846.

SOURCE – Fujisawa.

REFERENCES

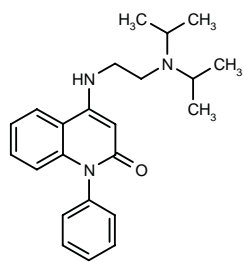
1. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Tricyclic cpds. as cGMP-PDE inhibitors*. WO 9921831.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

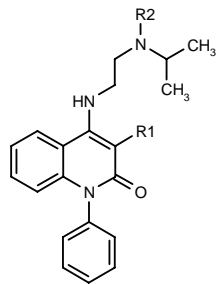
275468

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C23 H29 N3 O; Mol wt: 363.5021

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Compound	R1	R2	Formula
275469	CO2Et	i-Pr	C ₂₆ H ₃₃ N ₃ O ₃
275470	CO2Et	CH2CH2N(Et)2	C ₂₉ H ₄₀ N ₄ O ₃
275471	CN	i-Pr	C ₂₄ H ₂₈ N ₄ O
275473	CO2H	i-Pr	C ₂₄ H ₂₉ N ₃ O ₃

SOURCE – SS Pharmaceutical.

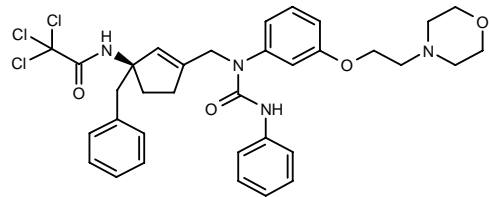
REFERENCES

1. Sata, Y. et al. (SS Pharmaceutical, Ltd.) *Substituted quinolone derivs. and medicines containing them*. JP 99071351.

IRRITABLE BOWEL SYNDROME THERAPY

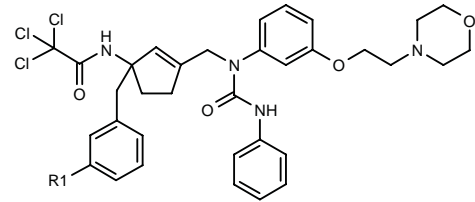
276499

N-[1(*S*)-Benzyl-3-[*N*-[3-[2-(4-morpholinyl)ethoxy]phenyl]-*N'*-phenylureidomethyl]-2-cyclopenten-1-yl]-2,2,2-trichloroacetamide



C34 H37 Cl3 N4 O4; Mol wt: 672.0493

ACTION – Motilin receptor antagonist that competes with erythromycin for the motilin receptor *in vitro* and suppresses smooth muscle contractions induced by motilin and erythromycin, with activity and potency comparable to OHM-11526 *in vitro*. It is expected to be particularly useful in the treatment of irritable bowel syndrome and esophageal reflux. Other specifically claimed cyclopentene derivatives are:



Compound	R1	Isomer	Formula
276500	H	R	C ₃₄ H ₃₇ Cl ₃ N ₄ O ₄
276501	Cl	S	C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄
276502	Cl		C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄
276503	Cl	R	C ₃₄ H ₃₆ Cl ₄ N ₄ O ₄

SOURCE – Ortho-McNeil.

REFERENCES

1. Chen, R.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Cyclopentene derivs. useful as antagonists of the motilin receptor*. WO 9921846.

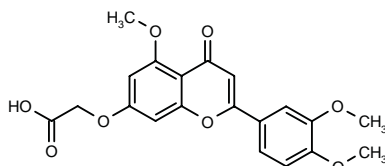
INFLAMMATORY BOWEL DISEASE THERAPY

DA-6034

276241

2-[2-(3,4-Dimethoxyphenyl)-5-methoxy-4-oxo-4*H*-1-benzopyran-7-yl]oxy]acetic acid

7-(Carboxymethoxy)-3',4',5-trimethoxyflavone



C20 H18 O8; Mol wt: 386.3542

ACTION – Flavonoid derivative with antiinflammatory activity in rat models of colitis. Compound given orally (0.3-30 mg/kg) to TNBS-treated rats significantly reduced macroscopic colonic damage, being more potent than sulfasalazine and prednisolone; it showed comparable effect to prednisolone on the reduction of colonic LTB₄ synthesis and myeloperoxidase activity. It was also active in HLA-B27 transgenic rats which develop spontaneous colitis. Potentially useful for the treatment of inflammatory bowel disease.

SOURCE – Dong-A.

REFERENCES

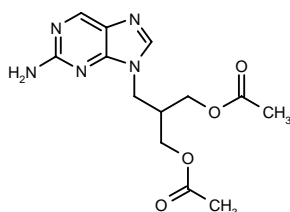
1. Yoo, M. et al. (Dong-A Pharmaceutical Co., Ltd.) *Gastroprotective flavone/flavone cpds. with therapeutic effect on inflammatory bowel disease*. WO 9804541.
2. Kim, Y.S. et al. *The oral therapy of flavonoids derivative DA-6034 in the experimental animal models of inflammatory bowel disease*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 4053.
3. Lee, J.J. et al. *Analysis of DA-6034, a new flavonoid derivative in biological fluids by HPLC*. Yakhak Hoeji 1998, 42(2): 149.
4. Son, M. et al. *Effect of DA-6034, a new flavonoid derivative, on TNBS-induced colitis in the rat*. Yakhak Hoeji 1998, 42(2): 205.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

275226

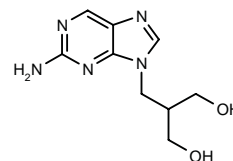
Acetic acid 3-acetoxy-2-(2-amino-9*H*-purin-9-ylmethyl)-propyl ester

9-[3-Acetoxy-2-(acetoxymethyl)propyl]-9*H*-purin-2-amine



C13 H17 N5 O4; Mol wt: 307.3083

ACTION – Antiviral agent for the treatment and prophylaxis of hepatitis B viral infection, with good oral bioavailability in rats (66.2%). Another specifically claimed purine acyclonucleoside derivative is:



275227: C9 H13 N5 O2

SOURCE – CSIRO, Clayton (AU).

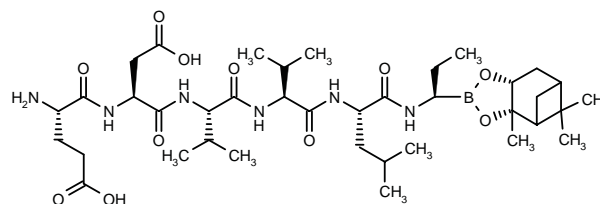
REFERENCES

1. Marcuccio, S.M. and Jarvis, K.E. (CSIRO [Commonwealth Scientific and Industrial Research Organisation]) *Purine acyclonucleosides as antiviral agents*. WO 9912927.

VRT-21493

274126

2(*R*)-(L-Glutamyl-L-aspartyl-L-valyl-L-valyl-L-leucyl-amino)propylboronic acid 2,6,6-trimethylbicyclo[3.1.1]-heptane-2(*S*),3(*R*)-diyl cyclic diester



C38 H65 B N6 O11; Mol wt: 792.7735

ACTION – Antiviral agent for the treatment of hepatitis C, a reversible inhibitor of hepatitis C virus NS3 protease (K_i = 10 nM).

SOURCE – Vertex.

REFERENCES

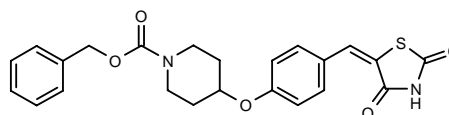
1. Perni, R.B. *In search of better inhibitors of the HCV NS3.4A protease domain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 265.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

275313

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]-piperidine-1-carboxylic acid benzyl ester



C23 H22 N2 O5 S; Mol wt: 438.5018

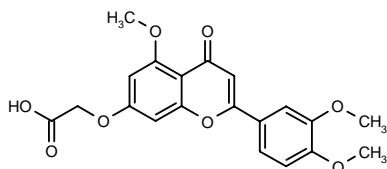
INFLAMMATORY BOWEL DISEASE THERAPY

DA-6034

276241

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7-(Carboxymethoxy)-3',4',5-trimethoxyflavone



C20 H18 O8; Mol wt: 386.3542

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SOURCE – Dong-A.

REFERENCES

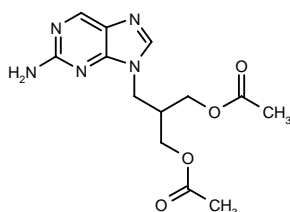
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4. Son, M. et al. *Effect of DA-6034, a new flavonoid derivative, on TNBS-induced colitis in the rat*. Yakhak Hoeji 1998, 42(2): 205.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

275226

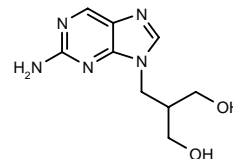
Acetic acid 3-acetoxy-2-(2-amino-9*H*-purin-9-ylmethyl)-propyl ester

9-[3-Acetoxy-2-(acetoxymethyl)propyl]-9*H*-purin-2-amine



C13 H17 N5 O4; Mol wt: 307.3083

ACTION – Antiviral agent for the treatment and prophylaxis of hepatitis B viral infection, with good oral bioavailability in rats (66.2%). Another specifically claimed purine acyclonucleoside derivative is:



275227: C9 H13 N5 O2

SOURCE – CSIRO, Clayton (AU).

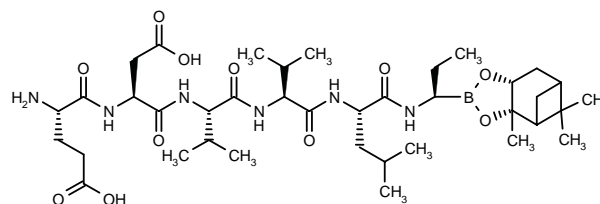
REFERENCES

1. Marcuccio, S.M. and Jarvis, K.E. (CSIRO [Commonwealth Scientific and Industrial Research Organisation]) *Purine acyclonucleosides as antiviral agents*. WO 9912927.

VRT-21493

274126

2(*R*)-(L-Glutamyl-L-aspartyl-L-valyl-L-valyl-L-leucyl-amino)propylboronic acid 2,6,6-trimethylbicyclo[3.1.1]-heptane-2(*S*),3(*R*)-diyl cyclic diester



C38 H65 B N6 O11; Mol wt: 792.7735

ACTION – Antiviral agent for the treatment of hepatitis C, a reversible inhibitor of hepatitis C virus NS3 protease (K_i = 10 nM).

SOURCE – Vertex.

REFERENCES

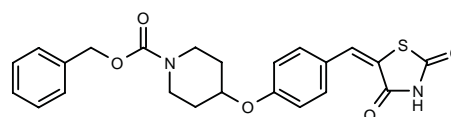
1. Perni, R.B. *In search of better inhibitors of the HCV NS3.4A protease domain*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 265.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

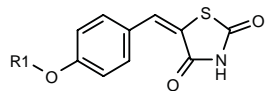
275313

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]-piperidine-1-carboxylic acid benzyl ester



C23 H22 N2 O5 S; Mol wt: 438.5018

ACTION – Antidiabetic agent shown to decrease blood glucose levels in *db/db* mice by 47 and 59%, respectively, at 30 and 100 mg/kg/day p.o. x 6 days, being more potent than troglitazone (28% reduction at 100 mg/kg/day p.o. x 6 days); at the dose of 100 mg/kg/day p.o., it also produced a 29% reduction in triglyceride levels. Also reported to be useful for the treatment of obesity, cardiovascular disorders such as hypertension, and hyperlipidemia. Other exemplified compounds include the following:



Compound	R1	Formula
275314	1-(PhCH2OCO)-4-Pip-CH2	C ₂₄ H ₂₄ N ₂ O ₅ S
275315	1-(PhCH2OCO)-2(S)-pyrrolidinyl	C ₂₃ H ₂₂ N ₂ O ₅ S
275316	1-(PhCH2NHCO)-4-Pip	C ₂₃ H ₂₃ N ₃ O ₄ S

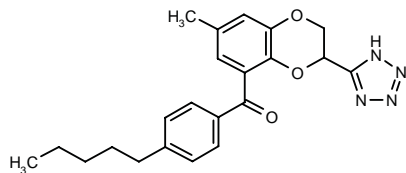
SOURCE – Dr. Reddy’s Research Foundation, Hyderabad (IN).

REFERENCES

1. Lohray, V.B. et al. (Dr. Reddy’s Research Foundation) *Antidiabetic cpds. having hypolipidaemic, antihypertensive properties, process for their preparation and pharmaceutical compsns. containing them.* US 5889025.

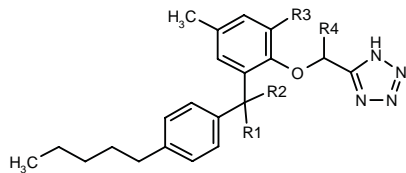
276226

1-[7-Methyl-3-(1*H*-tetrazol-5-yl)-2,3-dihydro-1,4-benzodioxin-5-yl]-1-(4-pentylphenyl)methanone



C22 H24 N4 O3; Mol wt: 392.4566

ACTION – Hypoglycemic and hypolipidemic agent, a peroxisome proliferator-activated receptor γ (PPAR γ) agonist proven to reduce blood glucose levels, free fatty acids and triglycerides in *db/db* mice at a dose of 100 mg/kg/day p.o. for 2 weeks. Potentially useful for the treatment of diabetes, obesity, syndrome X, hypercholesterolemia and hyperlipidemia, arteriosclerosis, circulatory diseases and ischemic heart disease. Other representative comopunds from this series of fused and nonfused benzenes are:



Compound	R1	R2	R3	R4	Formula
276227	H	H	-OCH2-		C ₂₂ H ₂₆ N ₄ O ₂
276228		-O-	H	H	C ₂₁ H ₂₄ N ₄ O ₂

SOURCE – Ono.

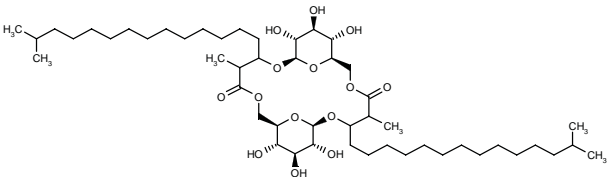
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1. Tajima, H. et al. (Ono Pharmaceutical Co., Ltd.) *Fused or nonfused benzene cpds.* WO 9915520.

GLUCOLIPSIN A

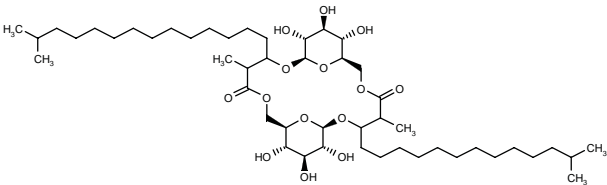
274867

[1*R*-(1 α ,8 α ,9 α ,10 β ,11 α ,12 α ,19 α ,20 α ,21 β ,22 α)]-9,10,11,20,21,22-Hexahydroxy-4,15-dimethyl-3,14-bis(13-methyltetradecyl)-2,6,13,17,23,24-hexaoxatricyclo[17.3.1.1^{8,12}]tetracosane-5,16-dione



C50 H92 O14; Mol wt: 917.2628

ACTION – Small-molecule glucokinase activator isolated from a butanol extract of *Streptomyces purpurogeniscleroticus* WC71634, that acts by preventing the inhibition of glucokinase by long-chain fatty acyl-CoA esters (FAC; RC₅₀ = 5.4 μ M). Compound also inhibited stearoyl-CoA oxidation in a concentration-dependent fashion and reduced free concentrations of stearoyl-CoA, which would be expected to result in deinhibition of glucokinase by stearoyl-CoA. Potentially useful for the treatment of diabetes. Another related compound, extracted from *Nocardia vaccinii* WC65712, is:



Glucolipin B [274868]: C49 H90 O14

SOURCE – Bristol-Myers Squibb.

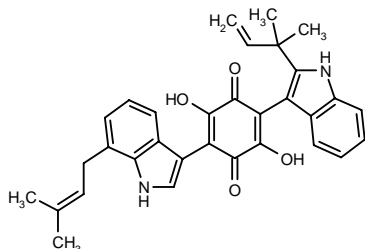
REFERENCES

1. Qian-Cutrone, J. et al. *Glucolipsin A and B, two new glucokinase activators produced by Streptomyces purpurogeniscleroticus and Nocardia vaccinii.* J Antibiot 1999, 52(3): 245.

L-783281**276013**

2,5-Dihydroxy-3-[2-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]-6-[7-(3-methyl-2-butenyl)-1*H*-indol-3-yl]-2,5-cyclohexadiene-1,4-dione

Demethylasterriquinone B-1



C32 H30 N2 O4; Mol wt: 506.5990

ACTION – Small-molecule insulin sensitizer produced by *Pseudomassaria* sp., with selectivity for activation of the insulin receptor (IR) versus the insulin-like growth factor-1 receptor (IGF-1R); compound selectively induced phosphorylation of the IR intracellular β -subunit (tyrosine domain). *In vivo* in two models of non-insulin-dependent diabetes mellitus in *db/db* and *ob/ob* mice, it significantly lowered blood glucose levels; in particular, in *ob/ob* mice doses of 5-20 mg/kg p.o. significantly and dose-dependently improved glucose tolerance and suppressed elevated plasma insulin levels.

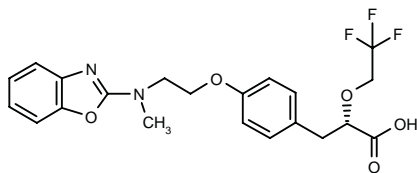
SOURCE – Merck & Co.

REFERENCES

1. Zhang, B. et al. *Discovery of a small molecule insulin mimetic with antidiabetic activity in mice*. *Science* 1999, 284(5416): 974.

SB-219994***237672**

3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]-phenyl]-2(*S*)-(2,2,2-trifluoroethoxy)propionic acid



C21 H21 F3 N2 O5; Mol wt: 438.4070

ACTION – Insulin sensitizer with the ability to potently inhibit [¹²⁵I]-SB-236636 binding to the peroxisomal proliferator-activated receptor (PPAR) γ 1 subtype; compound showed nanomolar affinity for rat and human adipocyte PPAR γ 1 receptors (IC_{50} = 0.36 and 1.5 nM, respectively). Compound exhibited antihyperglycemic activity in *ob/ob* mice (ED_{25} = 0.03 μ mol/kg p.o.).

SOURCE – SmithKline Beecham.

REFERENCES

1. Haigh, D. and Rami, H.K. (SmithKline Beecham plc) *Benzoxazoles and pyridine derivs. useful in the treatment of type II diabetes*. EP 772605, JP 98503508, WO 9604260, WO 9604261.

2. Smith, S.A. (SmithKline Beecham plc) *Use of an antagonist of PPAR- α and PPAR- γ for the treatment of syndrom X*. WO 9725042.

3. Young, P.W. et al. *Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor γ* . *J Pharmacol Exp Ther* 1998, 284(2): 751.

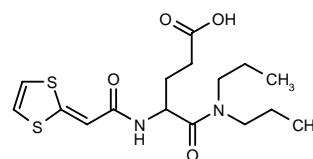
4. SmithKline Beecham: *annual report 1998/Q1 report 1999*. DailyDrugNews.com (Daily Essentials) 1999, April 27.

*Identified compound **237672** (see **235795**) Drug Data Report 1996, 018(07): 0627.

TREATMENT OF DIABETIC COMPLICATIONS

275353

N,N-Dipropyl-4-[2-(1,3-dithiol-2-ylidene)acetamido]glutamic acid



C16 H24 N2 O4 S2; Mol wt: 372.5076

ACTION – Agent for the treatment or prevention of diabetic complications that acts by inhibiting the formation of advanced glycosylation endproducts (AGEs) and protein crosslinks, as shown in an *in vitro* assay (IC_{50} = 30 μ g/ml vs. 30 μ g/ml for aminoguanidine).

SOURCE – SS Pharmaceutical.

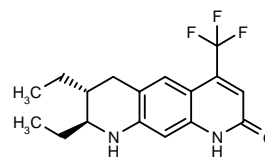
REFERENCES

1. Ishii, F. et al. (SS Pharmaceutical, Ltd.) *Dithiolylidene acetamide derivs*. EP 909758, JP 99124379.

TREATMENT OF MALE SEXUAL DYSFUNCTION

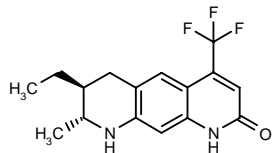
LG-121104**275496**

(\pm)-*trans*-7,8-Diethyl-4-(trifluoromethyl)-6,7,8,9-tetrahydropyrido[3,2-*g*]quinolin-2(1*H*)-one



C17 H19 F3 N2 O; Mol wt: 324.3441

ACTION – Nonsteroidal high-affinity ligand for the human androgen receptor (hAR; $K_i = 16$ nM in a receptor binding assay) with potent full agonist activity comparable to that of dihydrotestosterone in an hAR cotransfection assay ($EC_{50} = 3$ nM; 114% efficacy compared to dihydrotestosterone [100%]). Compound did not show agonist activity in human estrogen, glucocorticoid and mineralocorticoid receptor cotransfection assays, but it did show weak agonist activity at the human progesterone receptor ($EC_{50} = 260$ nM). Potentially useful as androgen replacement therapy in hypogonadal men and for the treatment of androgen-dependent diseases. Within this series of quinolinone analogues, the following is also included:



LG-121091 [275260]: C16 H17 F3 N2 O

SOURCE – Ligand.

REFERENCES

1. Edwards, J.P. et al. (Ligand Pharmaceuticals, Inc.) *Androgen receptor modulator cpds. and methods*. EP 918774, WO 9749709.

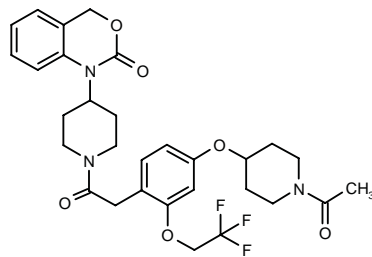
2. Zhi, L. et al. *Switching androgen receptor antagonists to agonists by modifying C-ring substituents on piperidino[3,2-g]quinolinone*. Bioorg Med Chem Lett 1999, 9(7): 1009.

**UTERINE STIMULANTS
AND TOCOLYTICS**

L-374943

276078

1-[1-[2-[4-(1-Acetylpiperidin-4-yloxy)-2-(2,2,2-trifluoroethoxy)phenyl]acetyl]piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



C30 H34 F3 N3 O6; Mol wt: 589.6076

ACTION – Oxytocin (OT) antagonist with high affinity for both cloned human OT receptors expressed in human embryonic kidney cells and rat uteri OT ($K_i = 1.4$ and 0.71 nM, respectively), showing good selectivity over human arginine vasopressin (AVP) receptors ($K_i = 740$ and 130 nM for human platelet V_{1a} and cloned human V_2 receptors, respectively). In functional studies in isolated rat uterine tissue, compound showed competitive antagonist activity against OT-induced contractions ($pA_2 = 9.2$). *In vivo*, it antagonized OT-induced contractions *in situ* in rat uterus ($ID_{50} = 0.06$ and 0.64 mg/kg after i.v. and i.d. administration, respectively). Compound showed a favorable pharmacokinetic profile in rats, with 19% oral bioavailability and good plasma levels ($C_{max} = 570$ nM)

after administration of 10 mg/kg p.o. Potentially useful for the treatment of preterm labor.

SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Tocolytic oxytocin receptor antagonists*. GB 2326410.

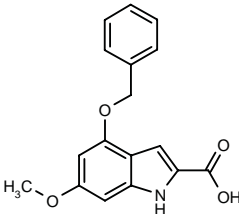
2. Williams, P.D. et al. *Nonpeptide oxytocin antagonists: Analogs of L-371,257 with improved potency*. Bioorg Med Chem Lett 1999, 9(9): 1311.

DERMATOLOGIC DRUGS

ACNE THERAPY

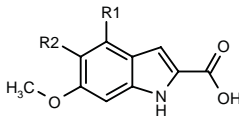
275179

4-Benzyloxy-6-methoxy-1H-indole-2-carboxylic acid

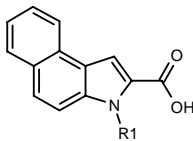


C17 H15 N O4; Mol wt: 297.3085

ACTION – Agent for the treatment of androgen-related disorders such as seborrhea, acne, hirsutism and androgenic alopecia that acts by inhibiting 5α -reductase, with marked selectivity for type 1 enzyme ($IC_{50} = 1-4$ μ M against type 1 enzyme; $IC_{50} > 100$ μ M against type 2 enzyme). Other specifically claimed indolecarboxylic acid derivatives include the following:

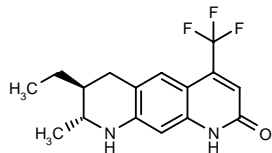


Compound	R1	R2	Formula
275180	3,5-(CF3)2-PhCH2O	H	C ₁₉ H ₁₃ F ₆ NO ₄
275181	H	3,5-(CF3)2-PhCH2O	C ₁₉ H ₁₃ F ₆ NO ₄
275182	H	3,4,5-(MeO)3-PhCH2O	C ₂₀ H ₂₁ NO ₇
275183	H	4-MeO-PhCH2O	C ₁₈ H ₁₇ NO ₅
275184	H	4-CN-PhCH2O	C ₁₈ H ₁₄ N ₂ O ₄



Compound	R1	Formula
275186	H	C ₁₁ H ₉ NO ₂
275187	Me	C ₁₄ H ₁₁ NO ₂
275188	CH2Ph	C ₂₀ H ₁₅ NO ₂
275189	3,5-(CF3)2-PhCH2	C ₂₂ H ₁₃ F ₆ NO ₂

ACTION – Nonsteroidal high-affinity ligand for the human androgen receptor (hAR; $K_i = 16$ nM in a receptor binding assay) with potent full agonist activity comparable to that of dihydrotestosterone in an hAR cotransfection assay ($EC_{50} = 3$ nM; 114% efficacy compared to dihydrotestosterone [100%]). Compound did not show agonist activity in human estrogen, glucocorticoid and mineralocorticoid receptor cotransfection assays, but it did show weak agonist activity at the human progesterone receptor ($EC_{50} = 260$ nM). Potentially useful as androgen replacement therapy in hypogonadal men and for the treatment of androgen-dependent diseases. Within this series of quinolinone analogues, the following is also included:



LG-121091 [275260]: C₁₆ H₁₇ F₃ N₂ O

SOURCE – Ligand.

REFERENCES

1. Edwards, J.P. et al. (Ligand Pharmaceuticals, Inc.) *Androgen receptor modulator cpds. and methods*. EP 918774, WO 9749709.

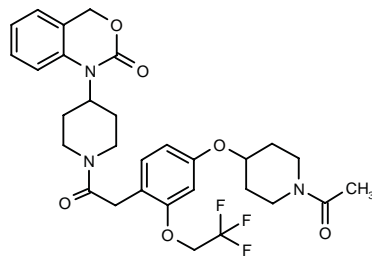
2. Zhi, L. et al. *Switching androgen receptor antagonists to agonists by modifying C-ring substituents on piperidino[3,2-g]quinolinone*. Bioorg Med Chem Lett 1999, 9(7): 1009.

**UTERINE STIMULANTS
AND TOCOLYTICS**

L-374943

276078

1-[1-[2-[4-(1-Acetylpiperidin-4-yloxy)-2-(2,2,2-trifluoroethoxy)phenyl]acetyl]piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



C₃₀ H₃₄ F₃ N₃ O₆; Mol wt: 589.6076

ACTION – Oxytocin (OT) antagonist with high affinity for both cloned human OT receptors expressed in human embryonic kidney cells and rat uteri OT ($K_i = 1.4$ and 0.71 nM, respectively), showing good selectivity over human arginine vasopressin (AVP) receptors ($K_i = 740$ and 130 nM for human platelet V_{1a} and cloned human V_2 receptors, respectively). In functional studies in isolated rat uterine tissue, compound showed competitive antagonist activity against OT-induced contractions ($pA_2 = 9.2$). *In vivo*, it antagonized OT-induced contractions *in situ* in rat uterus ($ID_{50} = 0.06$ and 0.64 mg/kg after i.v. and i.d. administration, respectively). Compound showed a favorable pharmacokinetic profile in rats, with 19% oral bioavailability and good plasma levels ($C_{max} = 570$ nM)

after administration of 10 mg/kg p.o. Potentially useful for the treatment of preterm labor.

SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Tocolytic oxytocin receptor antagonists*. GB 2326410.

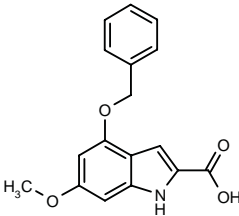
2. Williams, P.D. et al. *Nonpeptide oxytocin antagonists: Analogs of L-371,257 with improved potency*. Bioorg Med Chem Lett 1999, 9(9): 1311.

DERMATOLOGIC DRUGS

ACNE THERAPY

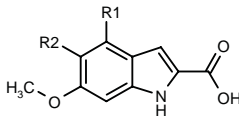
275179

4-Benzyloxy-6-methoxy-1H-indole-2-carboxylic acid

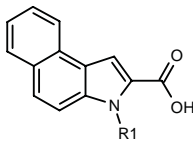


C₁₇ H₁₅ N O₄; Mol wt: 297.3085

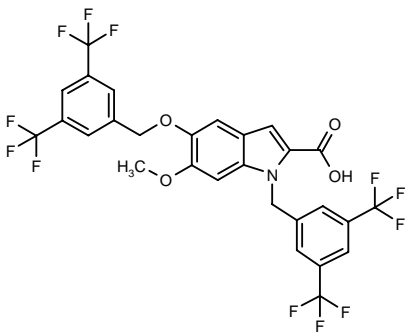
ACTION – Agent for the treatment of androgen-related disorders such as seborrhea, acne, hirsutism and androgenic alopecia that acts by inhibiting 5α -reductase, with marked selectivity for type 1 enzyme ($IC_{50} = 1-4$ μ M against type 1 enzyme; $IC_{50} > 100$ μ M against type 2 enzyme). Other specifically claimed indolecarboxylic acid derivatives include the following:



Compound	R1	R2	Formula
275180	3,5-(CF ₃) ₂ -PhCH ₂ O	H	C ₁₉ H ₁₃ F ₆ NO ₄
275181	H	3,5-(CF ₃) ₂ -PhCH ₂ O	C ₁₉ H ₁₃ F ₆ NO ₄
275182	H	3,4,5-(MeO) ₃ -PhCH ₂ O	C ₂₀ H ₂₁ NO ₇
275183	H	4-MeO-PhCH ₂ O	C ₁₈ H ₁₇ NO ₅
275184	H	4-CN-PhCH ₂ O	C ₁₈ H ₁₄ N ₂ O ₄



Compound	R1	Formula
275186	H	C ₁₃ H ₉ NO ₂
275187	Me	C ₁₄ H ₁₁ NO ₂
275188	CH ₂ Ph	C ₂₀ H ₁₅ NO ₂
275189	3,5-(CF ₃) ₂ -PhCH ₂	C ₂₂ H ₁₃ F ₆ NO ₂



275185: C28 H17 F12 N O4

SOURCE – L’Oreal.

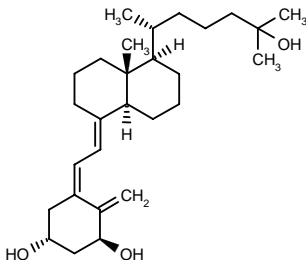
REFERENCES

1. Bernard, B. et al. (L’Oreal) *Indolecarboxylic cpds. and their use as pharmaceutical cpds.* WO 9912905.

ANTIPSORIATICS

276680

1 α ,26-Dihydroxy-D-homovitamin D₃



C28 H46 O3; Mol wt: 430.6684

ACTION – Vitamin D derivative useful for the treatment of vitamin D-dependent disorders such as psoriasis, leukemia, acne, seborrheic dermatitis, osteoporosis and hyperparathyroidism. It was significantly more potent than calcitriol in inducing HL-60 cell differentiation (EC₅₀ = 0.37 nM vs. 5 nM), while both compounds had a similar highest tolerated dose for calcemic liability in mice (0.5-0.6 μ g/kg/day s.c.).

SOURCE – Roche.

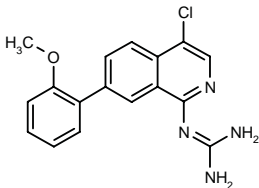
REFERENCES

1. Schneider, F. (Hoffmann-La Roche, Inc.) *Vitamin D deriv.* US 5905074.

WOUND-HEALING AGENTS

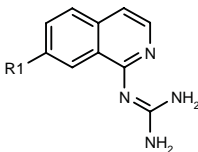
276165

N²-[4-Chloro-7-(2-methoxyphenyl)isoquinolin-1-yl]-guanidine



C17 H15 Cl N4 O; Mol wt: 326.7855

ACTION – Reversible and competitive urokinase (urinary-type plasminogen activator, or uPA) inhibitor (K_i = 63 nM) with > 1000- and 286-fold selectivity relative to tissue-type plasminogen activator (tPA) and plasmin. Potentially useful for wound healing, chronic dermal ulcers, angiogenesis, bone restructuring, embryo implantation in the uterus, cell infiltration into sites of inflammation, ovulation, spermatogenesis, tissue remodeling during wound repair and organ differentiation, fibrosis, local invasion of tumors into adjacent areas, secondary metastatic spread of tumor cells and tissue destruction in arthritis. Other representative compounds from this series of isoquinoline derivatives are:



Compound	R1	Formula
276166	Br	C ₁₀ H ₉ BrN ₄
276167	(E)-CH=CHPh	C ₁₈ H ₁₆ N ₄

SOURCE – Pfizer.

REFERENCES

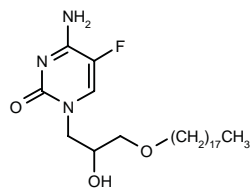
1. Barber, C.G. et al. (Pfizer Ltd.;Pfizer Inc.) *Isoquinolines as urokinase inhibitors.* WO 9920608.

CPR-1152

275386

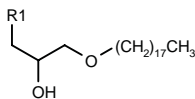
4-Amino-5-fluoro-1-[2-hydroxy-3-(octadecyloxy)propyl]-2(1*H*)-pyrimidinone

5-Fluoro-1-(2-hydroxy-3-octadecyloxypropyl)cytosine



C25 H46 F N3 O3; Mol wt: 455.6544

ACTION – Agent with tissue cell growth-promoting activity and potential for enhancing tissue repair and promoting wound healing. *In vitro*, compound was shown to stimulate the growth of cultured murine fibroblasts, as measured by an increase in DNA synthesis. *In vivo*, it increased granulation tissue formation in a guinea pig dorsal wound model. Other specifically claimed compounds within this series of aminoheterocycle-substituted glycerol derivatives are:



Compound	R1	Formula
275387	adenin-9-yl	C ₂₆ H ₄₇ N ₅ O ₂
275388	cytosin-1-yl	C ₂₅ H ₄₇ N ₃ O ₃

SOURCE – Clarion.

REFERENCES

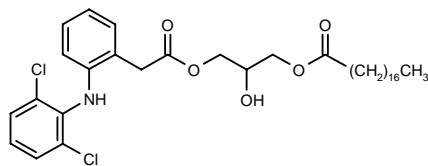
1. Nair, H.K. and Peterson, A.C. (Clarion Pharmaceuticals Inc.) *Aminoheterocycle-substd. glycerols*. US 5891881.

OTHER DERMATOLOGIC DRUGS

275406

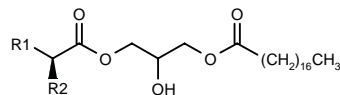
Octadecanoic acid 3-[2-[2-(2,6-dichlorophenylamino)-phenyl]acetoxyl]-2-hydroxypropyl ester

2-[2-(2,6-Dichlorophenylamino)phenyl]acetic acid 2-hydroxy-3-(octadecanoyloxy)propyl ester



C35 H51 Cl2 N O5; Mol wt: 636.6959

ACTION – Antiinflammatory and analgesic agent, a diclofenac derivative with a faster onset of action and longer duration than parent compound (1%) in a rat contusion edema model when applied topically at a concentration of 2%; when given orally in this model at a dose of 10 mg/kg, it exhibited comparable potency to diclofenac given at 5 mg/kg p.o. Compound exhibited lower toxicity in mice following a single oral dose of 400 mg/kg compared to diclofenac at 200 mg/kg. Other compounds from this series of glyceride derivatives of antiinflammatory agents include the following:



Compound	R1	R2	Formula
275407	H	1-(4-Cl-PhCO)-5-MeO-2-Me-3-indolyl	C ₄₀ H ₅₆ ClNO ₇
275408	Me	3-(PhCO)-Ph	C ₃₇ H ₅₄ O ₆
275409	Me	3-F-4-Ph-Ph	C ₃₆ H ₅₃ FO ₅

SOURCE – Ikeda Mohando.

REFERENCES

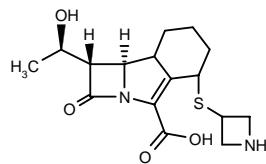
1. Nakamura, M. (Ikeda Mohando) *Fatty acid glyceride derivs. and glyceride derivs., and their preparation method*. JP 99043467.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

275477

(1*S*,8*bR*)-5-(Azetidin-3-ylsulfanyl)-1-[1(*R*)-hydroxyethyl]-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazeto[2,1-*a*]isoindole-4-carboxylic acid



C16 H22 N2 O4 S; Mol wt: 338.4258

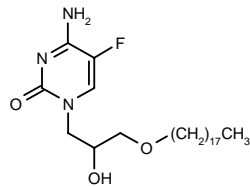
ACTION – Antibacterial agent, a representative compound from a series of trinems, wherein the following are also included:

CPR-1152

275386

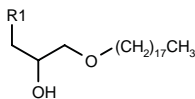
4-Amino-5-fluoro-1-[2-hydroxy-3-(octadecyloxy)propyl]-2(1*H*)-pyrimidinone

5-Fluoro-1-(2-hydroxy-3-octadecyloxypropyl)cytosine



C25 H46 F N3 O3; Mol wt: 455.6544

ACTION – Agent with tissue cell growth-promoting activity and potential for enhancing tissue repair and promoting wound healing. *In vitro*, compound was shown to stimulate the growth of cultured murine fibroblasts, as measured by an increase in DNA synthesis. *In vivo*, it increased granulation tissue formation in a guinea pig dorsal wound model. Other specifically claimed compounds within this series of aminoheterocycle-substituted glycerol derivatives are:



Compound	R1	Formula
275387	adenin-9-yl	C ₂₆ H ₄₇ N ₅ O ₂
275388	cytosin-1-yl	C ₂₅ H ₄₇ N ₃ O ₃

SOURCE – Clarion.

REFERENCES

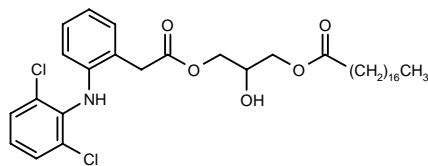
1. Nair, H.K. and Peterson, A.C. (Clarion Pharmaceuticals Inc.) *Aminoheterocycle-substd. glycerols*. US 5891881.

OTHER DERMATOLOGIC DRUGS

275406

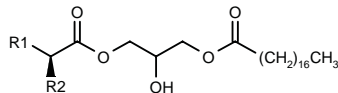
Octadecanoic acid 3-[2-[2-(2,6-dichlorophenylamino)-phenyl]acetoxyl]-2-hydroxypropyl ester

2-[2-(2,6-Dichlorophenylamino)phenyl]acetic acid 2-hydroxy-3-(octadecanoyloxy)propyl ester



C35 H51 Cl2 N O5; Mol wt: 636.6959

ACTION – Antiinflammatory and analgesic agent, a diclofenac derivative with a faster onset of action and longer duration than parent compound (1%) in a rat contusion edema model when applied topically at a concentration of 2%; when given orally in this model at a dose of 10 mg/kg, it exhibited comparable potency to diclofenac given at 5 mg/kg p.o. Compound exhibited lower toxicity in mice following a single oral dose of 400 mg/kg compared to diclofenac at 200 mg/kg. Other compounds from this series of glyceride derivatives of antiinflammatory agents include the following:



Compound	R1	R2	Formula
275407	H	1-(4-Cl-PhCO)-5-MeO-2-Me-3-indolyl	C ₄₀ H ₅₆ ClNO ₇
275408	Me	3-(PhCO)-Ph	C ₃₇ H ₅₄ O ₆
275409	Me	3-F-4-Ph-Ph	C ₃₆ H ₅₃ FO ₅

SOURCE – Ikeda Mohando.

REFERENCES

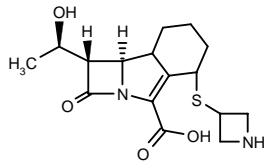
1. Nakamura, M. (Ikeda Mohando) *Fatty acid glyceride derivs. and glyceride derivs., and their preparation method*. JP 99043467.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

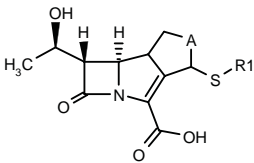
275477

(1*S*,8*bR*)-5-(Azetidin-3-ylsulfanyl)-1-[1(*R*)-hydroxyethyl]-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazeto[2,1-*a*]isoindole-4-carboxylic acid

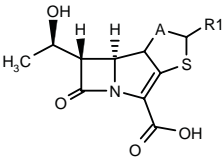


C16 H22 N2 O4 S; Mol wt: 338.4258

ACTION – Antibacterial agent, a representative compound from a series of trinems, wherein the following are also included:



Compound	R1	A	Formula
275478	1-(4,5-dihydro-2-imidazolyl)-4-Pip	-(CH2)2-	C ₂₁ H ₃₀ N ₄ O ₄ S
275479	1-[NH2C(=NH)]-3-pyrrolidinyl-CH2	-(CH2)2-	C ₁₉ H ₂₈ N ₄ O ₄ S
275480	5-[3-[NH2C(=NH)NH]-1-pyrrolidinyl-CO]-3-pyrrolidinyl	-(CH2)2-	C ₂₃ H ₃₄ N ₆ O ₅ S
275481	2-azetidiny-CH2	-(CH2)2-	C ₁₇ H ₂₄ N ₂ O ₄ S
275482	5-(3-NH2-1-pyrrolidinyl-CO)-3-pyrrolidinyl	-CH2-	C ₂₁ H ₃₀ N ₄ O ₅ S



Compound	R1	R2	Formula
275484	3-pyrrolidinyl	-(CH2)2-	C ₁₆ H ₂₂ N ₂ O ₄ S
275485	2-azetidiny-CH2	-(CH2)2-	C ₁₆ H ₂₂ N ₂ O ₄ S
275487	1-(4,5-dihydro-2-thiazolyl)-4-Pip	-CH2-	C ₁₉ H ₂₅ N ₃ O ₄ S ₂

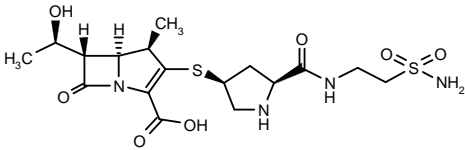
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *Triheterocyclic derivs.* JP 99060576.

275523

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-[*N*-(2-sulfamoylethyl)carbamoyl]pyrrolidin-3(*S*)-ylsulfany]-1-carbapen-2-em-3-carboxylic acid



C17 H26 N4 O7 S2; Mol wt: 462.5454

ACTION – Carbapenem antibiotic with potent activity against Gram-positive and Gram-negative bacteria and high stability to human renal dehydropeptidase I (DHP-I) as compared to other carbapenems such as meropenem. *In vivo*, compound exhibited higher bioavailability than meropenem and was shown to be more effective than this compound against *Streptococcus pyogenes* A77 and *Escherichia coli* 078 infections in mice, giving respective PD₅₀ values of 2.31 and 0.47 mg/kg s.c. vs. 7.16 and 1.24 mg/kg s.c. for meropenem.

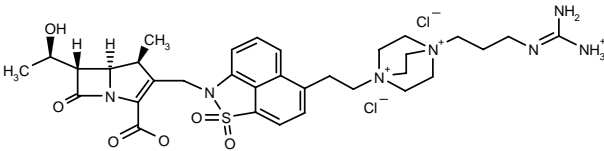
SOURCE – Korea Institute of Science and Technology, Seoul (KR).

REFERENCES

1. Park, S.W. et al. (Korea Institute of Science and Technology) *Carbapenem derivs. and a preparation method thereof.* WO 9914218.

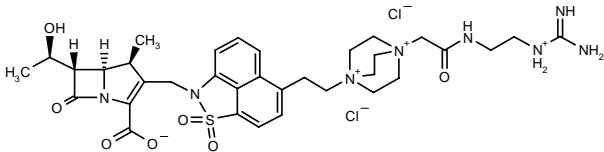
276158

(1*S*,5*R*,6*S*)-2-[6-[2-[4-(3-Guanidiniopropyl)-1,4-diazoniabicyclo[2.2.2]octan-1-yl]ethyl]-1,1-dioxo-naphtho[1,8-*cd*]isothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate dichloride

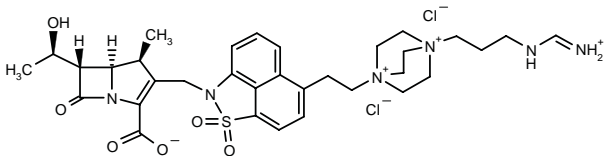


C33 H45 Cl2 N7 O6 S; Mol wt: 738.7335

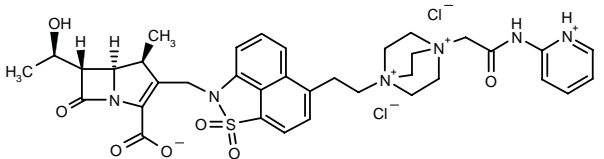
ACTION – Carbapenem antibiotic active against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS), and also active against Gram-negative pathogens. Other carbapenems in which the carbapenem nucleus is substituted at the 2-position with a naphthosultam linked through a CH₂ group include the following:



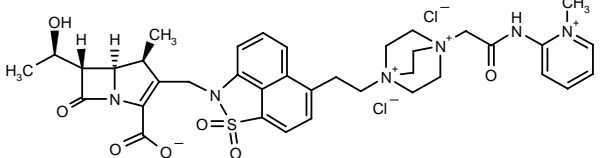
276159: C34 H46 Cl2 N8 O7 S



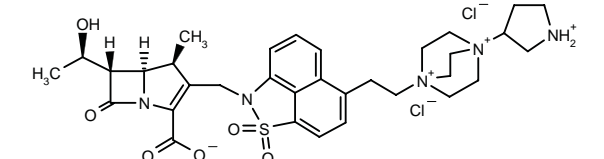
276160: C33 H44 Cl2 N6 O6 S



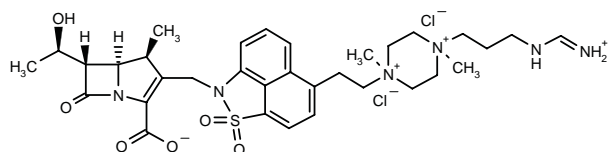
276161: C36 H42 Cl2 N6 O7 S



276162: C37 H44 Cl2 N6 O7 S



276163: C33 H43 Cl2 N5 O6 S



276164: C33 H46 Cl2 N6 O6 S

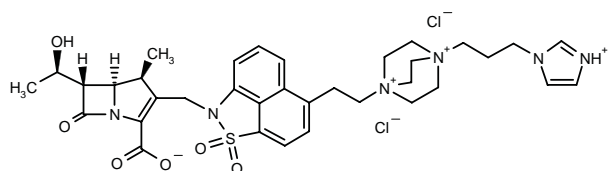
SOURCE – Merck & Co.

REFERENCES

1. Cama, L.D. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9920628.

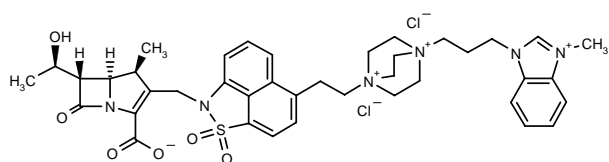
276327

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[6-[2-[4-[3-(1*H*-imidazol-3-ium-1-yl)propyl]-1,4-diazoniabicyclo[2.2.2]oct-1-yl]ethyl]-1,1-dioxonaphtho[1,8-*cd*]isothiazol-2-ylmethyl]-1-methyl-1-carbapen-2-em-3-carboxylate dichloride

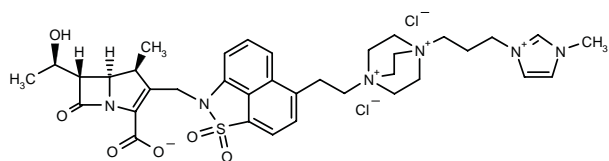


C35 H44 Cl2 N6 O6 S; Mol wt: 747.7406

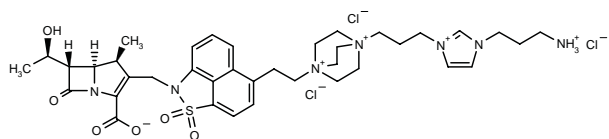
ACTION – Carbapenem antibiotic reported to be useful against Gram-positive bacteria, particularly methicillin-resistant staphylococci, and Gram-negative pathogens, while being relatively free of undesirable side effects. Other representative compounds include the following:



276328: C40 H48 Cl2 N6 O6 S



276329: C36 H46 Cl2 N6 O6 S



276330: C38 H52 Cl3 N7 O6 S

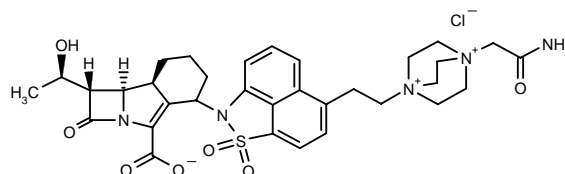
SOURCE – Merck & Co.

REFERENCES

1. Cama, L.D. et al. (Merck & Co., Inc.) *Antibacterial carbapenems, compsns. and methods of treatment.* WO 9920269.

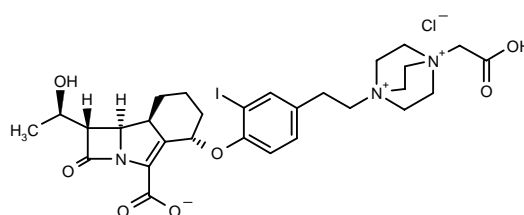
276331

(1*S*,8*aS*,8*bR*)-5-[6-[2-(4-Carbamoylmethyl-1,4-diazoniabicyclo[2.2.2]oct-1-yl)ethyl]-1,1-dioxonaphtho[1,8-*cd*]isothiazol-2-yl]-1-[1(*R*)-hydroxyethyl]-2-oxo-1,2,5,6,7,8,8*a*,8*b*-octahydroazeto[2,1-*a*]isoindole-4-carboxylate chloride

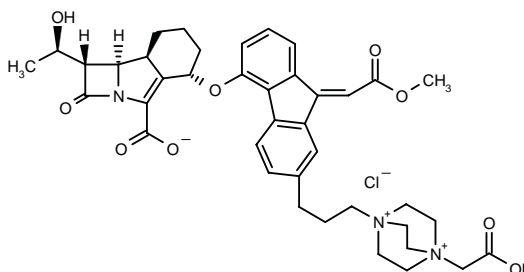


C33 H40 Cl N5 O7 S; Mol wt: 686.2260

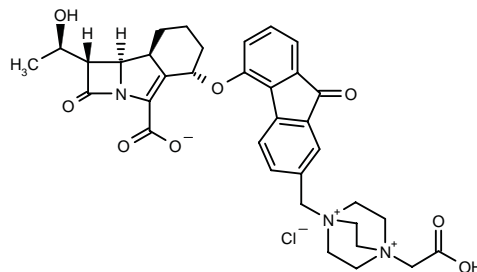
ACTION – Tricyclic carbapenem (trinem) antibiotic with a lipophilic side-chain necessary for activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Other representative compounds from this series are:



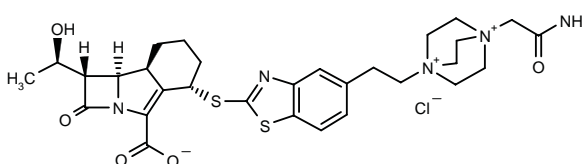
276332: C29 H37 Cl I N3 O7



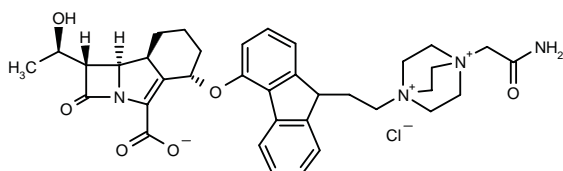
276337: C40 H46 Cl N3 O9



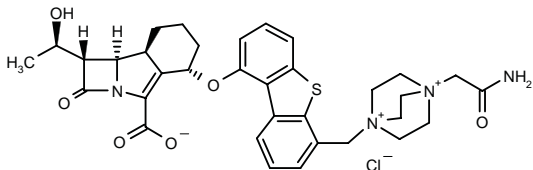
276338: C35 H38 Cl N3 O8



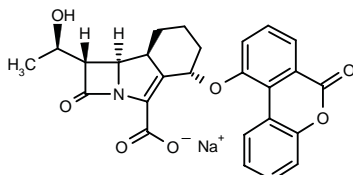
276339: C30 H38 Cl N5 O5 S2



276340: C36 H43 Cl N4 O6



276341: C34 H39 Cl N4 O6 S



276342: C26 H22 N Na O7

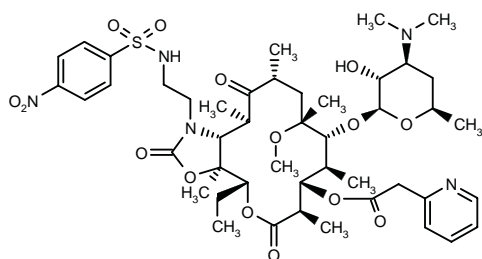
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. and Hammond, M.L. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. and methods of treatment.* WO 9920270.

276487

11-Deoxy-3-des(cladinosyl)-11-[2-(4-nitrophenyl-sulfonamido)ethylamino]-3-O-(2-pyridylacetyl)-6-O-methylerythromycin A 11-N,12-O-cyclic carbamate



C46 H67 N5 O15 S; Mol wt: 962.1213

ACTION – Macrolide antibiotic with strong antibacterial activity against not only erythromycin-sensitive but also erythromycin-resistant bacteria. Compound displayed high activity against Gram-positive pathogens such as *Staphylococcus aureus* 209P-JC (MIC = 0.10 µg/ml), *S. aureus* Smith (MIC = 0.20 µg/ml), *Staphylococcus epidermidis* IID 866 (MIC = 0.025 µg/ml), *Enterococcus faecalis* CSJ 1212 (MIC = 0.10 µg/ml) and *Streptococcus pneumoniae* BM 225 and BM 205 (MIC = 0.78 µg/ml and 1.56 µg/ml, respectively). A representative compound from a series of erythromycin A 11,12-carbamates.

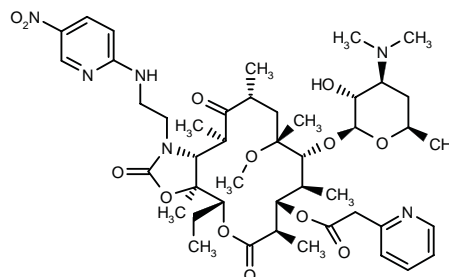
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A, 11,12-carbamate derivs.* WO 9921869.

276489

11-Deoxy-3-des(cladinosyl)-11-[2-[N-(5-nitro-2-pyridyl)-amino]ethylamino]-3-O-(2-pyridylacetyl)-6-O-methylerythromycin A 11-N,12-O-cyclic carbamate



C45 H66 N6 O13; Mol wt: 899.0454

ACTION – Macrolide antibiotic with strong antibacterial activity against not only erythromycin-sensitive but also erythromycin-resistant bacteria. Compound displayed high activity against Gram-positive pathogens such as *Staphylococcus aureus* 209P-JC (MIC = 0.10 µg/ml), *S. aureus* Smith (MIC = 0.20 µg/ml), *Staphylococcus epidermidis* IID 866 (MIC = 0.10 µg/ml), *Enterococcus faecalis* CSJ 1212 (MIC = 0.10 µg/ml) and *Streptococcus pneumoniae* BM 225 and BM 205 (MIC = 0.20 µg/ml and 1.56 µg/ml, respectively). A representative compound from a series of erythromycin A 11,12-carbamates.

SOURCE – Taisho.

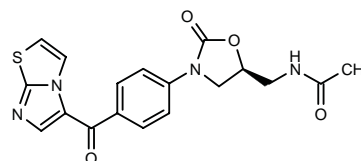
REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A 11,12-carbamate derivs.* WO 9921870.

ANTIBACTERIAL DRUGS

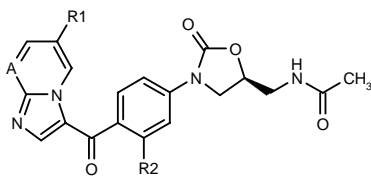
275202

N-[3-[4-(Imidazo[2,1-b]thiazol-5-ylcarbonyl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C18 H16 N4 O4 S; Mol wt: 384.4144

ACTION – Antibacterial agent with a broad spectrum of activity against Gram-positive bacteria including methicillin-resistant/quinolone-resistant *Staphylococcus aureus* (MIC = 0.5 µg/ml) and methicillin-resistant coagulase-negative staphylococci (MIC = 0.06 µg/ml). In particular, test compound is reported to be active against various strains exhibiting resistance to vancomycin and against *Enterococcus faecium* strains resistant to both aminoglycosides and clinically used β-lactams. Other specifically claimed aminomethyl-oxooxazolidinyl-benzene derivatives include the following:



Compound	R1	R2	A	Formula
275203	Cl	H	N	C ₁₉ H ₁₆ ClN ₅ O ₄
275204	SCH ₂ CH ₂ OH	H	CH	C ₂₂ H ₂₂ N ₄ O ₅ S
275205	F	H	CH	C ₂₀ H ₁₇ FN ₄ O ₄
275206	H	F	CH	C ₂₀ H ₁₇ FN ₄ O ₄
275207	Cl	H	CH	C ₂₀ H ₁₇ ClN ₄ O ₄
275208	Br	H	CH	C ₂₀ H ₁₇ BrN ₄ O ₄

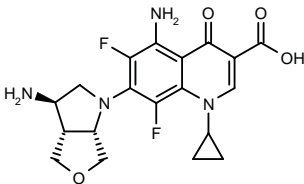
SOURCE – AstraZeneca.

REFERENCES

1. Mills, S.D. (Zeneca Ltd.) *Aminomethyl oxoxazolidinyl benzene derivs.* WO 9911642.

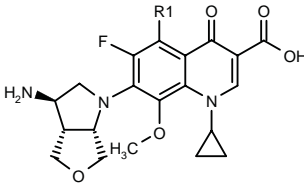
275424

5-Amino-7-[(3*R**,3*aR**,6*aS**)-3-aminohexahydro-1*H*-furo[3,4-*b*]pyrrol-1-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H20 F2 N4 O4; Mol wt: 406.3870

ACTION – Quinolone antibacterial agent active *in vitro* against *Staphylococcus aureus* 209P JC-1 (MIC = 0.025 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 0.05 µg/ml), *Salmonella typhimurium* S-9 (MIC = 0.05 µg/ml), *Klebsiella pneumoniae* (MIC = 0.1 µg/ml) and *Pseudomonas aeruginosa* 12 (MIC = 0.39 µg/ml). *In vivo*, it was effective in a murine model of *P. aeruginosa* 12 systemic infection, with an ED₅₀ value of 3.21 mg/kg i.v. Within this series of quinolonecarboxylic acid derivatives, the following are also included:



Compound	R1	Formula
275425	H	C ₂₀ H ₂₂ FN ₃ O ₅
275426	NH ₂	C ₂₀ H ₂₃ FN ₄ O ₅

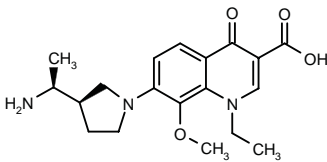
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Tojima, M. et al. (Dainippon Pharmaceutical Co., Ltd.) *Pyridone carboxylic acid derivs., their esters or salts.* JP 99060578.

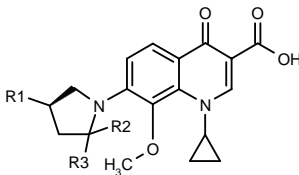
275617

7-[3(*R*)-[1(*S*)-Aminoethyl]pyrrolidin-1-yl]-1-ethyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

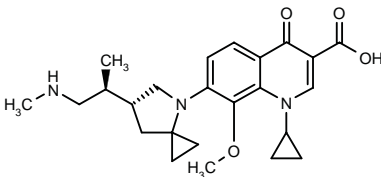


C19 H25 N3 O4; Mol wt: 359.4235

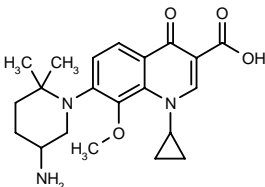
ACTION – Quinolone antibacterial agent reported to possess better activity against certain quinolone-resistant bacteria compared to ciprofloxacin, with MIC values up to about 500 times lower. Within this series of specifically claimed quinolone derivatives, the following are also included:



Compound	R1	R2	R3	Formula
275618	C(Me)2NH ₂	H	H	C ₂₁ H ₂₇ N ₃ O ₄
275619	(<i>S</i>)-CH(Me)NHMe	Me	Me	C ₂₃ H ₃₁ N ₃ O ₄
275620	C(Me)2NHMe	Et	H	C ₂₄ H ₃₃ N ₃ O ₄



275621: C24 H31 N3 O4



275622: C21 H27 N3 O4

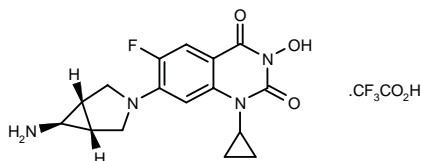
SOURCE – Procter & Gamble.

REFERENCES

1. Ledoussal, B. et al. (The Procter & Gamble Co.) *Antimicrobial quinolones, their compsns. and uses.* WO 9914214.

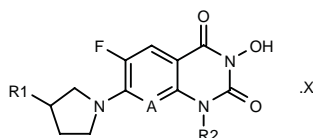
276414

(1 α ,5 α ,6 α)-7-[6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-1-cyclopropyl-6-fluoro-3-hydroxyquinazoline-2,4(1*H*,3*H*)-dione trifluoroacetate



C16 H17 F N4 O3 . C2 H F3 O2; Mol wt: 446.3552

ACTION – Antibacterial agent, a quinolone mimic found to inhibit DNA gyrase (IC₅₀ = 0.76 μ M) and topoisomerase IV (IC₅₀ = 28 μ M) and to exhibit activity against Gram-positive and Gram-negative bacteria such as *Escherichia coli* B90 (MIC = 0.25 μ g/ml), *Staphylococcus aureus* 29213 (MIC = 4.0 μ g/ml) and *Streptococcus pyogenes* C203 (MIC = 2.0 μ g/ml). Reported to not be highly cytotoxic to mammalian cells, indicating selectivity for bacteria. Other compounds from this series of 7-substituted quinazoline-2,4-diones include the following:



Compound	R1	R2	A	X	Formula
276427	NH2	Et	N	CF3CO2H	C ₁₃ H ₁₆ FN ₅ O ₃ ·C ₂ HF ₃ O ₂
276429	H	cyclopropyl	CH		C ₁₅ H ₁₆ FN ₃ O ₃
276431	NH2	cyclopropyl	CH		C ₁₅ H ₁₇ N ₄ O ₃
276432	H	4-F-Ph	N		C ₁₇ H ₁₄ F ₂ N ₄ O ₃

SOURCE – Warner-Lambert.

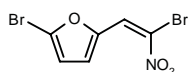
REFERENCES

- Domagala, J.M. et al. (Warner-Lambert Co.) *Novel 7-substd. quinazolin-2,4-diones useful as antibacterial agents*. WO 9921840.

G1

272555

2-Bromo-5-(2-bromo-2-nitrovinyl)furan



C6 H3 Br2 N O3; Mol wt: 296.9017

ACTION – Antimicrobial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria, anaerobic bacteria, yeast and filamentous fungi. Its rank order of activity is: filamentous fungi (MIC₉₀ = 0.5-4 mg/l) = yeast (MIC₉₀ = 2-4 mg/l) > anaerobic bacteria (MIC₉₀ = 0.5-16 mg/l) = Gram-positive bacteria (MIC₉₀ = 4-32 mg/l) = Gram-negative bacteria (MIC₉₀ = 1-32 mg/l). In particular, compound showed good activity against *Candida albicans* (MIC₅₀ = 2 mg/l), *Candida tropicalis* (MIC₅₀ = 4 mg/l), *Streptococcus pyogenes* (MIC₅₀ = 4

mg/l), *Staphylococcus aureus* (MIC₅₀ = 8 mg/l), *Enterococcus* spp. (MIC₅₀ = 16 mg/l), *Klebsiella* spp. (MIC₅₀ = 16 mg/l) and *Escherichia coli* (MIC₅₀ = 16 mg/l). Compound inhibited DNA, RNA and protein synthesis, as well as certain key metabolic processes. G1 is formulated for topical use, although formulations for ophthalmic and vaginal application have also been developed and intestinal and inhaled formulations are being investigated. Currently being evaluated in phase I/II clinical trials.

SOURCES – Universidad Central de Las Villas, Santa Clara (CU); York Medical.

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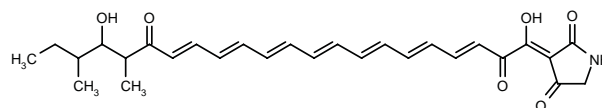
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- Blondeau, J.M. et al. *In vitro evaluation of G1: A novel antimicrobial compound*. Int J Antimicrob Agents 1999, 11(2): 163.
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- Ramos, A. et al. *Activity of a nitroalkene derivative, 1-(5-bromofur-2-yl)-2-bromo-2-nitroethene, in the Salmonella/microsome assay and the mouse bone marrow micronucleus test*. Mutat Res 1997, 390(3): 233.
- York Medical: *Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, Feb 12.

ANTIFUNGAL AGENTS

F-10778

276098

3(Z)-[(3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*)-1,19-Dihydroxy-18,20-dimethyl-2,17-dioxodocosa-3,5,7,9,11,13,15-heptaenylidene]pyrrolidine-2,4-dione



C28 H33 N O6; Mol wt: 479.5697

ACTION – Antifungal agent isolated from *Tapesia* sp. SANK 18896 (FERM BP-6090) with MIC₈₀ values of 2, 2-4, 2, 16-32 and 8-16 μ g/ml, respectively, when tested against *Candida albicans* ATCC90028, *Candida parapsilosis* ATCC90018, *Candida tropicalis* SANK59263, *Cryptococcus neoformans* SANK59863 and *Aspergillus fumigatus* SANK10662. Compound is devoid of antibacterial activity, as demonstrated by MIC₈₀ values > 64 μ g/ml when tested against *Staphylococcus aureus* SANK70668 and *Escherichia coli* SANK70569.

SOURCE – Sankyo.

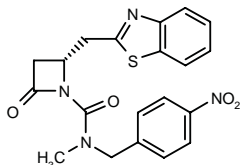
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ANTIVIRAL DRUGS

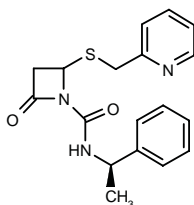
274145²

2-(R)-(1,3-Benzothiazol-2-ylmethyl)-N-methyl-N-(4-nitrobenzyl)-4-oxoazetidine-1-carboxamide



C₂₀ H₁₈ N₄ O₄ S; Mol wt: 410.4522

ACTION – An inhibitor of human cytomegalovirus (HCMV) protease (IC₅₀ = 0.7 μM) with a good selectivity profile. In cell culture, compound inhibited HCMV replication with an IC₅₀ of 30 μM. Another monocyclic β-lactam is:



274144^{1,2}: C₁₈ H₁₉ N₃ OS

SOURCE – Boehringer Ingelheim.

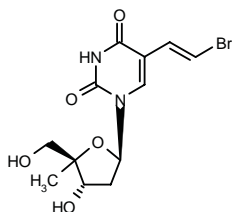
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4'-MethylBVDU

274857

5-(2-Bromovinyl)-2'-deoxy-4'-C-methyluridine



C₁₂ H₁₅ Br N₂ O₅; Mol wt: 347.1635

ACTION – Antiviral agent, a 4'-C-methylnucleoside with potent *in vitro* activity against varicella-zoster virus (ED₅₀ = 0.77 ng/ml) and herpes simplex virus type 1 (HSV-1; ED₅₀ = 5.3 ng/ml) and type 2 (HSV-2; ED₅₀ = 0.26 μg/ml). Compound also exhibited cytotoxic activity (IC₅₀ = 0.45 μg/ml) against human T-cell leukemia CCRF-HSB-2.

SOURCE – Yamasa Shoyu.

REFERENCES

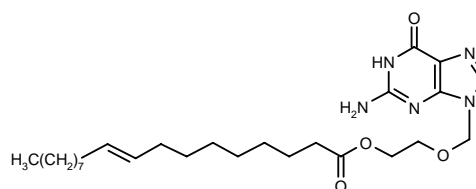
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P-4010*

198423

9-[2-[9(E)-Octadecenoyloxy]ethoxymethyl]guanine

Aciclovir elaidate



C₂₆ H₄₃ N₅ O₄; Mol wt: 489.6567

ACTION – Antiviral agent active against herpes simplex virus type 2 (HSV-2), with the ability to reduce the clinical symptoms of both primary and recurrent genital herpes in female guinea pigs; compound (40 mg/kg/day i.p. or 200 mg/kg/day p.o) was more effective than aciclovir or penciclovir in reducing the severity and the duration of genital herpes, and was associated with a reduction in spontaneous, recurrent HSV-2 lesions in the vaginal area in animals recovered from primary HSV-2 infection.

SOURCE – Norsk Hydro.

REFERENCES

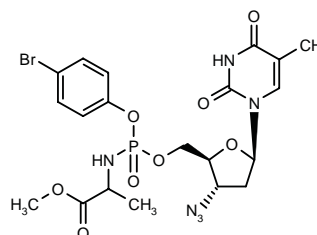
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2. Jennings, R. et al. *Evaluation of a novel, anti-herpes simplex virus compound, acyclovir elaidate (P-4010), in the female guinea pig model of genital herpes*. Antimicrob Agents Chemother 1999, 43(1): 53.

*Identified compound **198423** (see **Acyclovir oleate**) Drug Data Report 1993, 015(08): 0767.

AIDS MEDICINES

273308

3'-Azido-5'-O-[4-bromophenoxy[1-(methoxycarbonyl)-ethylamino]phosphoryl]-3'-deoxythymidine



C₂₀ H₂₄ Br N₆ O₈ P; Mol wt: 587.3216

ACTION – Anti-HIV agent, a phenyl phosphate derivative of zidovudine (AZT) proven to be 5-fold more potent than the latter in inhibiting HIV replication in thymidine kinase-deficient CEM cells (IC_{50} = 0.04 and 0.1-0.2 μ M, respectively) and at least as potent as AZT in inhibiting HIV replication in peripheral blood mononuclear cells. Compound did not show cytotoxicity against CEM cells at up to 100 μ M.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

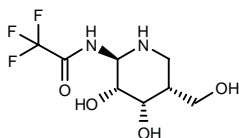
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1. Jan, S.-T. et al. AZT-5'-(p-bromophenyl methoxyalaninyl phosphate) as a potent and non-toxic anti-human immunodeficiency virus agent. *Antivir Chem Chemother* 1999, 10(1): 47.

2. Venkatachalam, T.K. et al. Enhancing effects of a mono-bromo substitution at the para position of the phenyl moiety on the metabolism and anti-HIV activity of d4T-phenyl methoxyalaninyl phosphate derivatives. *Bioorg Med Chem Lett* 1998, 8(22): 3121.

274771

(2*R*,3*R*,4*S*,5*R*)-*N*-[3,4-Dihydroxy-5-(hydroxymethyl)piperidin-2-yl]-2,2,2-trifluoroacetamide



C₈ H₁₃ F₃ N₂ O₄; Mol wt: 258.1947

$[\alpha]_D^{23} +39^\circ$ (*c* 0.64, MeOH).

ACTION – Glycosidase inhibitor with particularly strong activity against α -D- and β -D-galactosidase from *Aspergillus niger* (IC_{50} = 0.1 and 0.05 μ g/ml, respectively), β -D-glucosidase from almonds (IC_{50} = 0.14 μ g/m) and α -D-*N*-acetylgalactosaminidase from chicken liver (IC_{50} = 0.65 μ g/ml). Potentially useful for the treatment of disorders including AIDS, cancer and diabetes.

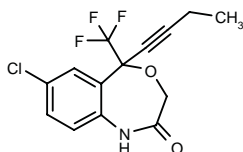
SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

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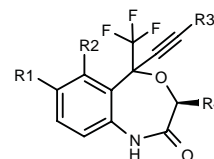
275212

5-(1-Butynyl)-7-chloro-5-trifluoromethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-2-one

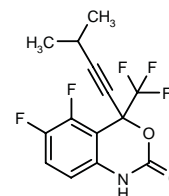


C₁₄ H₁₁ Cl F₃ N O₂; Mol wt: 317.6929

ACTION – Antiviral agent for AIDS, an inhibitor of HIV reverse transcriptase (IC_{50} < 12 μ M). Within this series of specifically claimed 5,5-disubstituted-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one derivatives, the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
275213	Cl	H	i-Pr	H	5S	C ₁₅ H ₁₃ ClF ₃ NO ₂
275215	Cl	H	cyclopropyl	H		C ₁₅ H ₁₁ ClF ₃ NO ₂
275216	Cl	H	cyclopropyl	Me	3S,5S	C ₁₆ H ₁₃ ClF ₃ NO ₂
275217	F	F	cyclopropyl	cyclopropyl	3R*,5R*	C ₁₆ H ₁₄ F ₅ NO ₂
275218	-OCH ₂ O-		cyclopropyl	Me	8R*,10R*	C ₁₇ H ₁₄ F ₃ NO ₄



275214: C₁₄ H₁₀ F₅ N O₂

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Cocuzza, A.J. and Rodgers, J.D. (DuPont Pharmaceuticals Co.) 5,5-Disubst.-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-ones useful as HIV reverse transcriptase inhibitors. WO 9911635.

275275

[Asp³⁸]-TAT

ACTION – Transdominant TAT variant with reduced transactivation capabilities as compared to wild-type TAT and TAT function-inhibitory activity, especially useful for the prevention or treatment of HIV infection.

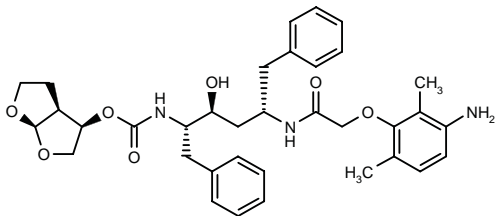
SOURCE – Transgene.

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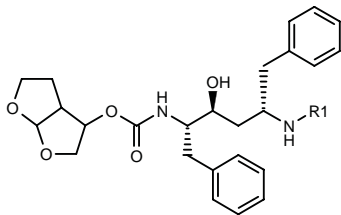
276660

N-[(1*S*,2*S*,4*S*)-4-[2-(3-Amino-2,6-dimethylphenoxy)acetamido]-1-benzyl-2-hydroxy-5-phenylpentyl]carbamic acid (3*R*,3*aS*,6*aR*)-perhydrofuro[2,3-*b*]furan-3-yl ester

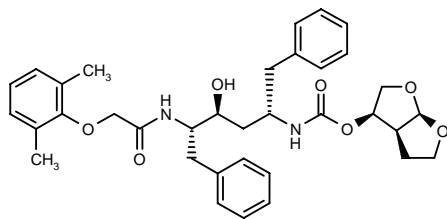


C35 H43 N3 O7; Mol wt: 617.7387

ACTION – Anti-HIV agent, a retroviral protease inhibitor affording 87% inhibition of HIV-1 protease at 0.5 nM in a fluorogenic assay; it exhibited potent antiviral activity in infected MT-4 cells ($EC_{50} < 0.032 \mu M$) and low cytotoxicity ($CTC_{50} > 100 \mu M$). Other representative compounds include the following:



Compound	R1	Isomer	Formula
276662	2,6-(Me)2-PhOCH2CO	3 <i>R</i> ,3 <i>aS</i> ,6 <i>aR</i>	C ₃₅ H ₄₂ N ₂ O ₇
276665	4,6-(Me)2-5-benzimidazolyl-OCH2CO	3 <i>R</i> ,3 <i>aS</i> ,6 <i>aR</i>	C ₃₆ H ₄₂ N ₄ O ₇
276667	4,6-(Me)2-2-oxo-2,3-dihydro-5-benzimidazolyl-OCH2CO	3 <i>R</i> ,3 <i>aS</i> ,6 <i>aR</i>	C ₃₆ H ₄₂ N ₄ O ₈
276668	2- <i>i</i> -Pr-4-thiazolyl-CH2OCO-L-Val-		C ₃₈ H ₅₀ N ₄ O ₆ S
276671	2- <i>i</i> -Pr-4-thiazolyl-CH2N(Me)CO-D-Val-	3 <i>R</i> ,3 <i>aS</i> ,6 <i>aR</i>	C ₃₉ H ₅₃ N ₅ O ₇ S



276663: C35 H42 N2 O7

SOURCE – Abbott.

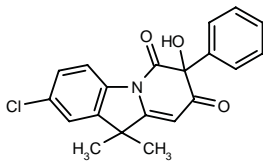
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BCH-1

275308

2-Chloro-7-hydroxy-10,10-dimethyl-7-phenylpyrido[1,2-*a*]indole-6,8(7*H*,10*H*)-dione



C20 H16 Cl N O3; Mol wt: 353.8034

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor ($IC_{50} = 4 \mu M$) with anti-HIV-1 activity ($IC_{50} = 0.58 \mu M$) and low cytotoxicity ($CC_{50} = 22.6 \mu M$) in MT-4 cells. Compound showed antiviral activity similar to nevirapine against HIV-1 cultured in cell lines and in human peripheral blood mononuclear cells (PBMCs) infected with clinical isolates of HIV-1; neither compound was active against HIV-2. BCH-1 was active against viruses resistant to the nucleoside reverse transcriptase inhibitors zidovudine, didanosine and lamivudine. A lead compound for the development of a more potent and/or selective molecule for use in the combination therapy of HIV infection.

SOURCE – BioChem Pharma.

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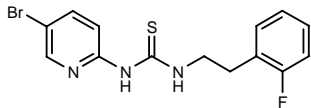
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HI-240¹⁻⁵

274160

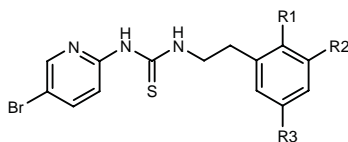
N-(5-Bromo-2-pyridinyl)-*N*'-[2-(2-fluorophenyl)ethyl]thiourea

F-PBT



C14 H13 Br F N3 S; Mol wt: 354.2457

ACTION – Anti-HIV agent, a potent non-nucleoside HIV reverse transcriptase inhibitor (NNRTI; $IC_{50} = 0.6 \mu M$ using recombinant RT). Compound inhibited HIV replication in human peripheral mononuclear cells with an IC_{50} value of $< 1 \text{ nM}$ and a selectivity index of $> 100,000$, and it was more active than zidovudine (AZT) or trovirdine. Other related compounds are:



Compound	R1	R2	R3	Formula
HI-253 [270091] ²⁻⁵	Cl	H	H	C ₁₄ H ₁₃ BrClN ₃ S
270092 ⁴	H	Cl	H	C ₁₄ H ₁₃ BrClN ₃ S
HI-236 [274161] ¹⁻³	OMe	H	OMe	C ₁₆ H ₁₈ BrN ₃ O ₂ S
HI-241 [274162] ²⁻⁴	H	F	H	C ₁₄ H ₁₃ BrFN ₃ S

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

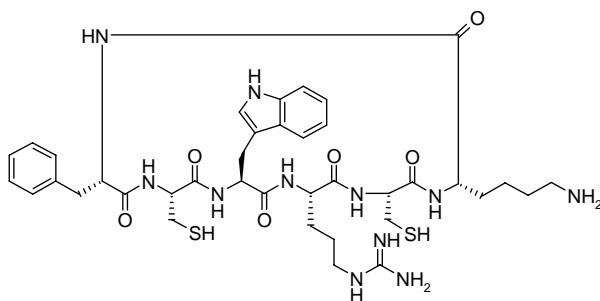
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5. Vig, R. et al. *Synthesis and structure-activity relationship of novel phenethylthiazolyl derivatives.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 177.

RB-2121

275793

Cyclo[L-phenylalanyl-L-cysteinyl-D-tryptophyl-L-arginyl-L-cysteinyl-L-lysine]



C38 H53 N11 O6 S2; Mol wt: 824.0397

ACTION – Anti-HIV agent, a cyclic peptide proven to inhibit HIV-1 replication in CEM-4 cells with similar potency when added before or after virus infection (IC₅₀ = 30 and 43 μM, respectively), indicating that it does not interfere with HIV-1 cell entry. Compound appear to acts at an early step in the retrovirus life cycle by inducing a reduction in transcribed DNA levels through inhibition of the nucleocapsid protein NCp7 interaction with reverse transcriptase. No cytotoxicity was observed at up to 150 μM. It represents a potential new lead compound in a new class of anti-HIV-1 agents.

SOURCE – Rhône-Poulenc Rorer.

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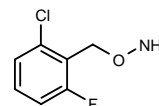
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RD6-Y664

263620

2-(Aminooxymethyl)-1-chloro-3-fluorobenzene

O-(2-Chloro-6-fluorobenzyl)hydroxylamine



C7 H7 Cl F N O; Mol wt: 175.5893

ACTION – Anti-HIV benzylhydroxylamine derivative, an inhibitor of HIV-1 replication, as demonstrated against HIV-1 strain IIIB in MT-4 cells (IC₅₀ = 1.6 μg/ml; CC₅₀ = 62 μg/ml). It also inhibited the replication of other HIV-1 and HIV-2 strains including a non-nucleoside reverse transcriptase inhibitor-resistant mutant and a nucleoside RT inhibitor-resistant mutant (EC₅₀ = 1.3-6.6 μg/ml) in acutely infected cells; compound did not affect HIV-1 production in chronically infected cells. It did not inhibit the HIV-1 reverse transcriptase or protease, nor the binding of anti-CXCR4 antibody to CXCR4 or the gp120-CD4 interaction, suggesting that it may inhibit HIV replication via a novel mechanism.

SOURCES – Rational Drug Design Laboratories, Fukushima (JP); Yamanouchi.

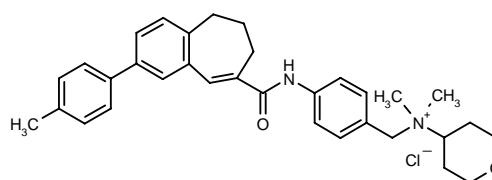
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TAK-779

275823

N,N-Dimethyl-*N*-[4-[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarboxamido]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride



C33 H39 Cl N2 O2; Mol wt: 531.1361

ACTION – Anti-HIV agent, a highly potent and selective chemokine CCR5 receptor antagonist with the ability to completely inhibit [125 I]-RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) binding in CCR5-expressing CHO cells (IC_{50} = 1.4 nM; K_i = 1.1 nM) and to block CCR5-mediated Ca^{2+} signaling. It also inhibited the binding of macrophage inflammatory protein-1 α (MIP-1 α) and MIP-1 β in these cells (IC_{50} = 1.0 nM), but it had no effect on ligand binding in CHO cells expressing CCR1, CCR2B, CCR3 or CCR4 receptors. Compound was shown to inhibit R5 HIV-1 replication in MAGI-CCR5 cells (EC_{50} = 1.2 nM; EC_{90} = 5.7 nM), as well as the replication of R5 HIV-1 clinical isolates in peripheral blood mononuclear cells, with EC_{50} s ranging from 1.6 to 3.7 nM; it showed no cytotoxicity to host cells and was inactive against T-cell line-tropic HIV-1. Currently being evaluated in animal toxicology and pharmacokinetic studies with the aim of entering it into phase I trials.

SOURCE – Takeda.

REFERENCES

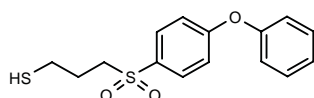
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

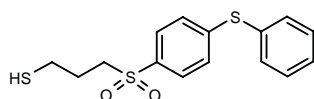
275243

3-(4-Phenoxyphenylsulfonyl)-1-propanethiol



C15 H16 O3 S2; Mol wt: 308.4204

ACTION – Potent matrix metalloproteinase (MMP) inhibitor with high selectivity for collagenase 3 and collagenase 2 (MMP-13 and MMP-8; IC_{50} = 2 and 36 nM, respectively) over stromelysin 1 and collagenase 1 (MMP-3 and MMP-1; IC_{50} = 150 and > 10,000 nM, respectively). Potentially useful in the therapy of osteoarthritis for the prevention of the degradation and loss of cartilage. Another sulfone MMP inhibitor is:



275245: C15 H16 O2 S3

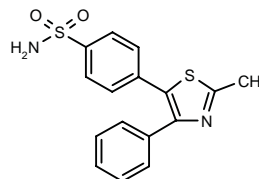
SOURCE – Searle.

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275575

4-(2-Methyl-4-phenylthiazol-5-yl)benzenesulfonamide



C16 H14 N2 O2 S2; Mol wt: 330.4306

ACTION – Cyclooxygenase type 2 (COX-2) inhibitor (IC_{50} = 0.038 μ M against human COX-2) with good selectivity over human COX-1 (IC_{50} = 34 μ M). In the rat air pouch assay, compound given orally at dose of 2 mg/kg inhibited the carrageenan-induced inflammatory response by 59%. Potentially useful for the treatment of inflammation, fever and pain.

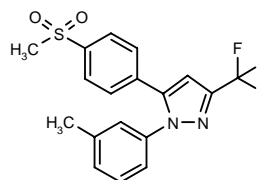
SOURCE – Searle.

REFERENCES

1. Talley, J.J. et al. (G.D. Searle & Co.) *Subst. thiazoles for the treatment of inflammation*. EP 772606, JP 98504542, US 5668161, WO 9603392.
2. Carter, J.S. et al. *Synthesis and activity of sulfonamide-substituted 4,5-diaryl thiazoles as selective cyclooxygenase-2 inhibitors*. Bioorg Med Chem Lett 1999, 9(8): 1171.

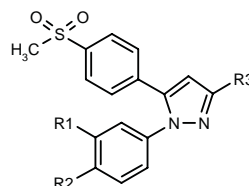
275649

1-(3-Methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole



C18 H15 F3 N2 O2 S; Mol wt: 380.3885

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2) proven active in the adjuvant arthritis assay in rats (> 60% inhibition of secondary lesions at a dose of 1.0 mg/kg p.o. once a day for 23 days). Other specifically claimed 1,5-diphenyl-pyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
275650	Br	Me	CHF2	C ₁₈ H ₁₅ BrF ₂ N ₂ O ₂ S
275651	Me	F	CN	C ₁₈ H ₁₄ FN ₃ O ₂ S
275652	Cl	OMe	Cl	C ₁₇ H ₁₄ Cl ₂ N ₂ O ₃ S

ACTION – Anti-HIV agent, a highly potent and selective chemokine CCR5 receptor antagonist with the ability to completely inhibit [125 I]-RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) binding in CCR5-expressing CHO cells (IC_{50} = 1.4 nM; K_i = 1.1 nM) and to block CCR5-mediated Ca^{2+} signaling. It also inhibited the binding of macrophage inflammatory protein-1 α (MIP-1 α) and MIP-1 β in these cells (IC_{50} = 1.0 nM), but it had no effect on ligand binding in CHO cells expressing CCR1, CCR2B, CCR3 or CCR4 receptors. Compound was shown to inhibit R5 HIV-1 replication in MAGI-CCR5 cells (EC_{50} = 1.2 nM; EC_{90} = 5.7 nM), as well as the replication of R5 HIV-1 clinical isolates in peripheral blood mononuclear cells, with EC_{50} s ranging from 1.6 to 3.7 nM; it showed no cytotoxicity to host cells and was inactive against T-cell line-tropic HIV-1. Currently being evaluated in animal toxicology and pharmacokinetic studies with the aim of entering it into phase I trials.

SOURCE – Takeda.

REFERENCES

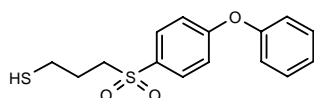
1. Baba, M. et al. A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. *Proc Natl Acad Sci USA* 1999, 96(10): 5698.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

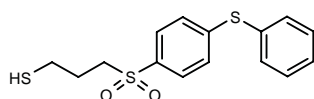
275243

3-(4-Phenoxyphenylsulfonyl)-1-propanethiol



C15 H16 O3 S2; Mol wt: 308.4204

ACTION – Potent matrix metalloproteinase (MMP) inhibitor with high selectivity for collagenase 3 and collagenase 2 (MMP-13 and MMP-8; IC_{50} = 2 and 36 nM, respectively) over stromelysin 1 and collagenase 1 (MMP-3 and MMP-1; IC_{50} = 150 and > 10,000 nM, respectively). Potentially useful in the therapy of osteoarthritis for the prevention of the degradation and loss of cartilage. Another sulfone MMP inhibitor is:



275245: C15 H16 O2 S3

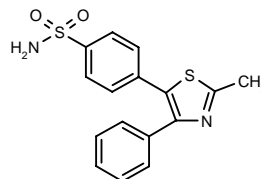
SOURCE – Searle.

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1. Freskos, J.N. et al. (Monsanto Co.) Thiol sulfone metalloprotease inhibitors. WO 9803164.
2. Freskos, J.N. et al. Discovery of a novel series of selective MMP inhibitors: Identification of the γ -sulfone-thiols. *Bioorg Med Chem Lett* 1999, 9(7): 943.

275575

4-(2-Methyl-4-phenylthiazol-5-yl)benzenesulfonamide



C16 H14 N2 O2 S2; Mol wt: 330.4306

ACTION – Cyclooxygenase type 2 (COX-2) inhibitor (IC_{50} = 0.038 μ M against human COX-2) with good selectivity over human COX-1 (IC_{50} = 34 μ M). In the rat air pouch assay, compound given orally at dose of 2 mg/kg inhibited the carrageenan-induced inflammatory response by 59%. Potentially useful for the treatment of inflammation, fever and pain.

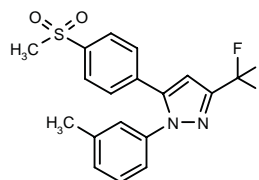
SOURCE – Searle.

REFERENCES

1. Talley, J.J. et al. (G.D. Searle & Co.) Substd. thiazoles for the treatment of inflammation. EP 772606, JP 98504542, US 5668161, WO 9603392.
2. Carter, J.S. et al. Synthesis and activity of sulfonamide-substituted 4,5-diaryl thiazoles as selective cyclooxygenase-2 inhibitors. *Bioorg Med Chem Lett* 1999, 9(8): 1171.

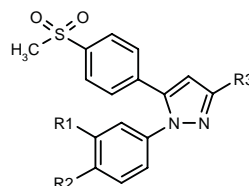
275649

1-(3-Methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole



C18 H15 F3 N2 O2 S; Mol wt: 380.3885

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2) proven active in the adjuvant arthritis assay in rats (> 60% inhibition of secondary lesions at a dose of 1.0 mg/kg p.o. once a day for 23 days). Other specifically claimed 1,5-diphenylpyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
275650	Br	Me	CHF2	C ₁₈ H ₁₅ BrF ₂ N ₂ O ₂ S
275651	Me	F	CN	C ₁₈ H ₁₄ FN ₃ O ₂ S
275652	Cl	OMe	Cl	C ₁₇ H ₁₄ Cl ₂ N ₂ O ₃ S

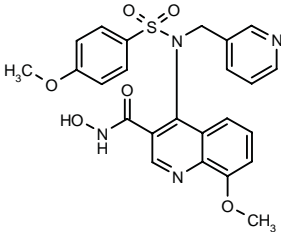
SOURCE – Fujisawa.

REFERENCES

1. Nakamura, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) 1,5-Diphenylpyrazole derivs. WO 9915505.

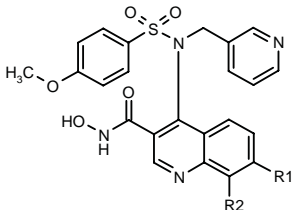
275764

8-Methoxy-4-[N-(4-methoxyphenylsulfonyl)-N-(3-pyridyl-methyl)amino]quinoline-3-carboxylic acid

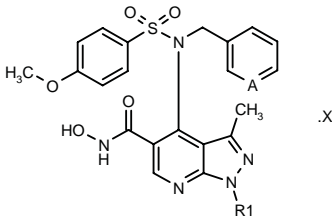


C24 H22 N4 O6 S; Mol wt: 494.5258

ACTION – Nonpeptide inhibitor of matrix metalloproteinases (MMPs) such as fibroblast collagenase (MMP-1; IC₅₀ = 46 nM), gelatinase B (MMP-9; IC₅₀ = 2 nM) and collagenase 3 (MMP-13; IC₅₀ = 1 nM), as well as of tumor necrosis factor-α-converting enzyme (TACE; IC₅₀ = 226 nM). *In vivo*, it was shown to inhibit MMP-13 in rodents following oral administration of 50 mg/kg. Potentially useful for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disorders, graft rejection and HIV infection. Other compounds from this series of heteroaryl hydroxamic acid derivatives include the following:



Compound	R1	R2	Formula
275765	CF3	H	C ₂₄ H ₁₉ F ₃ N ₄ O ₅ S
275766	H	2-thienyl	C ₂₇ H ₂₂ N ₄ O ₅ S ₂



Compound	R1	A	X	Formula
275767	Me	CH		C ₂₃ H ₂₃ N ₅ O ₅ S
275768	Me	N		C ₂₂ H ₂₂ N ₆ O ₅ S
275769	Me	N	HCl	C ₂₂ H ₂₂ N ₆ O ₅ S.HCl
275770	Ph	N	HCl	C ₂₇ H ₂₄ N ₆ O ₅ S.HCl

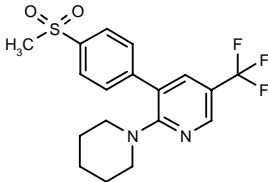
SOURCE – American Home Products.

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1. Levin, J.I. et al. (American Cyanamid Co.) The preparation and use of ortho-sulfonamido bicyclic heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors. WO 9918076.

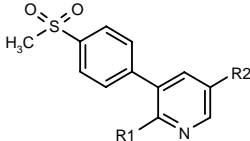
275884

3-(4-Methylsulfonylphenyl)-2-(1-piperidinyl)-5-(trifluoromethyl)pyridine



C18 H19 F3 N2 O2 S; Mol wt: 384.4201

ACTION – Antiinflammatory agent with reduced potential for inducing gastrointestinal side effects by virtue of its selective inhibition of cyclooxygenase type 2 (COX-2) relative to COX-1. Within this series of specifically claimed 2-aminopyridine derivatives, the following are also included:



Compound	R1	R2	Formula
275885	hexahydro-1-azepinyl	CF3	C ₁₉ H ₂₁ F ₃ N ₂ O ₂ S
275886	2(S)-(HOCH2)-1-pyrrolidinyl	CF3	C ₁₈ H ₁₉ F ₃ N ₂ O ₃ S
275887	2(S)-(AcOCH2)-1-pyrrolidinyl	CF3	C ₂₀ H ₂₁ F ₃ N ₂ O ₄ S
275888	2(S)-(MeOCH2)-1-pyrrolidinyl	Cl	C ₁₈ H ₂₁ ClN ₂ O ₃ S
275889	4-OH-1-Pip	CF3	C ₁₈ H ₁₉ F ₃ N ₂ O ₃ S
275890	3-OH-1-Pip	CF3	C ₁₈ H ₁₉ F ₃ N ₂ O ₃ S
275891	4,4-(F)2-1-Pip	CF3	C ₁₈ H ₁₇ F ₅ N ₂ O ₂ S

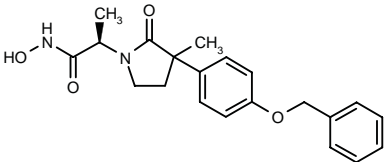
SOURCE – Merck Frosst.

REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) 2-Aminopyridines as inhibitors of cyclooxygenase-2. WO 9914195.

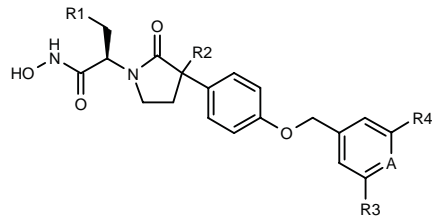
276000

N-Hydroxy-2(R)-[3-methyl-2-oxo-3-[4-(benzyloxy)phenyl]-pyrrolidin-1-yl]propionamide

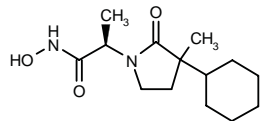


C21 H24 N2 O4; Mol wt: 368.4306

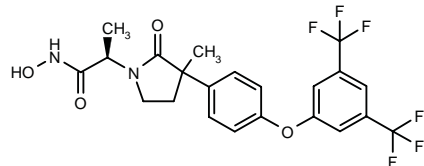
ACTION – An inhibitor of matrix metalloproteinases (MMPs) including stromelysin 1, aggrecanase and tumor necrosis factor convertase (TNF-C), and of the production of TNF, useful in the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, cancer, multiple sclerosis, psoriasis, cardiovascular disorders, fever, cachexia, acute infection, shock, graft-versus-host reaction and HIV infection. Other specifically claimed compounds within this series of lactam derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
276002	H	Me	Me	NHAc	CH	C ₂₄ H ₂₉ N ₃ O ₅
276004	i-Pr	Me	Me	Me	N	C ₂₅ H ₃₃ N ₃ O ₄
276005	(CH ₂) ₃ NH ₂	Me	Cl	Cl	N	C ₂₃ H ₂₈ Cl ₂ N ₄ O ₄
276006	t-BuOCONH-CH ₂ CONHCH ₂	Me	Me	Me	N	C ₃₀ H ₄₁ N ₅ O ₇
276007	H	NH ₂	Me	Me	CH	C ₂₂ H ₂₇ N ₃ O ₄
276008	H	4-Pyr-NHCONH	Cl	Cl	N	C ₂₅ H ₂₄ Cl ₂ N ₆ O ₅
276009	i-Pr	2-benzimidazolyl-NHCONH	Cl	Cl	N	C ₃₀ H ₃₁ Cl ₂ N ₇ O ₅



276001: C₁₄ H₂₄ N₂ O₃



276003: C₂₂ H₂₀ F₆ N₂ O₄

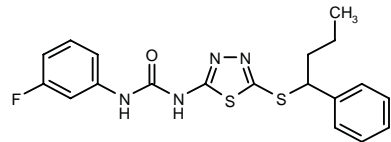
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Duan, J. et al. (DuPont Pharmaceuticals Co.) *Novel lactam metalloprotease inhibitors*. WO 9918074.

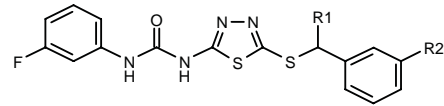
276246

N-(3-Fluorophenyl)-*N'*-[5-(1-phenylbutylsulfanyl)-1,3,4-thiadiazol-2-yl]urea



C₁₉ H₁₉ F N₄ O S₂; Mol wt: 402.5161

ACTION – LFA-1 and Mac-1 β_2 integrin inhibitor (IC₅₀ = 0.3 and 0.51 μ M, respectively, against binding with ICAM-1) potentially useful as an antiinflammatory agent for the treatment of hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury and inflammatory bowel disease, among other disorders. Other exemplified thiadiazolyl ureas include the following:



Compound	R1	R2	Formula
276248	H	t-BuOCO	C ₂₁ H ₂₁ FN ₄ O ₃ S ₂
276250	Et	H	C ₁₈ H ₁₇ FN ₄ OS ₂

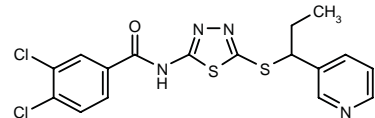
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Gammill, R.B. et al. (Pharmacia & Upjohn Co.) *Antiinflammatory thiadiazolyl ureas which act as LFA-1 and MAC-1 inhibitors*. WO 9920617.

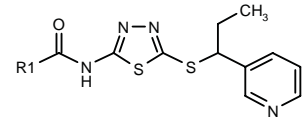
276253

3,4-Dichloro-*N*-[5-[1-(3-pyridinyl)propylsulfanyl]-1,3,4-thiadiazol-2-yl]benzamide



C₁₇ H₁₄ Cl₂ N₄ O S₂; Mol wt: 425.3626

ACTION – LFA-1 and Mac-1 β_2 integrin inhibitor (IC₅₀ = 0.2 and 2.4 μ M, respectively, for binding to ICAM-1) potentially useful as an antiinflammatory agent for hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury and inflammatory bowel disease, among other disorders. Other exemplified thiadiazole amides include the following:



Compound	R1	Formula
276254	CH(Me)Ph	C ₁₉ H ₂₀ N ₄ OS ₂
276256	3,5-(F) ₂ -Ph	C ₁₇ H ₁₄ F ₂ N ₄ OS ₂
276257	3,5-(MeO) ₂ -Ph	C ₁₉ H ₂₀ N ₄ O ₃ S ₂

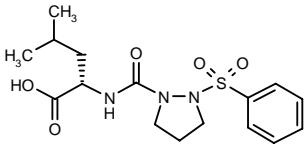
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Gammill, R.B. et al. (Pharmacia & Upjohn Co.) *Thiadiazoles amides useful as antiinflammatory agents*. WO 9920618.

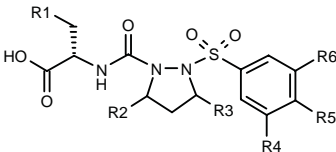
276304

N-[2-(Phenylsulfonyl)pyrazolidin-1-ylcarbonyl]-L-leucine

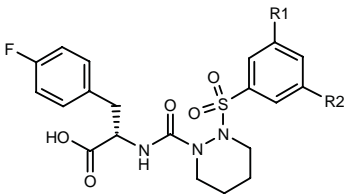


C16 H23 N3 O5 S; Mol wt: 369.4397

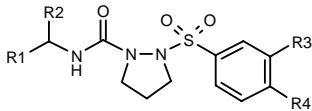
ACTION – Cell adhesion inhibitor, a VLA-4 (very late antigen-4, CD49d/CD29, $\alpha_4\beta_1$) and/or $\alpha_4\beta_7$ (LPAM-1, $\alpha_4\beta_p$) integrin antagonist found to block the binding of VLA-4 and/or $\alpha_4\beta_7$ to their ligands (i.e., VCAM-1 and fibronectin). Potentially useful for the treatment of disorders characterized by cell adhesion and activation such as asthma, multiple sclerosis, inflammatory bowel disease, allergic rhinitis, atherosclerosis and inflammation. Other specifically claimed azapeptide acids include the following:



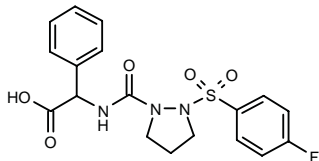
Compound	R1	R2	R3	R4	R5	R6	Formula
276305	2-Naph	H	H	Cl	H	Cl	C ₂₃ H ₂₁ Cl ₂ N ₃ O ₅ S
276306	Ph	(R)-Me	H	Cl	H	Cl	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₅ S
276307	Ph	(S)-Me	H	Cl	H	Cl	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₅ S
276308	Ph	H	Me	Cl	H	Cl	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₅ S
276311	Ph	H	H	Cl	H	Cl	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₅ S
276312	Pr	H	H	H	F	H	C ₁₈ H ₂₂ FN ₃ O ₅ S
276314	4-Ph-Ph	H	H	H	F	H	C ₂₅ H ₂₄ FN ₃ O ₅ S
276320	Ph	H	H	H	F	H	C ₁₉ H ₂₀ FN ₃ O ₅ S
276321	4-F-Ph	H	H	H	H	F	C ₁₉ H ₁₉ F ₂ N ₃ O ₅ S
276322	4-(2-CN-Ph)- -Ph	H	H	H	H	F	C ₂₆ H ₂₃ FN ₄ O ₅ S
276323	4-(2-MeO-Ph)- -Ph	H	H	Cl	H	Cl	C ₂₆ H ₂₅ Cl ₂ N ₃ O ₅ S



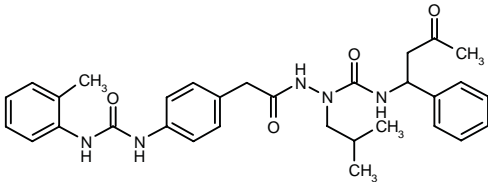
Compound	R1	R2	Formula
276309	Cl	Cl	C ₂₀ H ₂₀ Cl ₂ FN ₃ O ₅ S
276310	F	H	C ₂₀ H ₂₁ F ₂ N ₃ O ₅ S



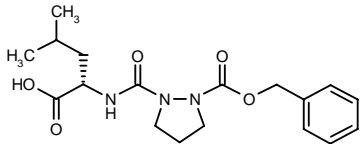
Compound	R1	R2	R3	R4	Formula
276315	CH ₂ CO ₂ H	Me	H	F	C ₁₄ H ₁₈ FN ₃ O ₅ S
276316	CH ₂ CO ₂ H	CH ₂ Ph	H	F	C ₂₀ H ₂₂ FN ₃ O ₅ S
276317	CH ₂ CO ₂ H	i-Bu	H	F	C ₁₇ H ₂₄ FN ₃ O ₅ S
276318	CH ₂ CO ₂ H	Ph	H	F	C ₁₉ H ₂₀ FN ₃ O ₅ S
276319	CH(Me)CO ₂ H	H	H	F	C ₁₄ H ₁₈ FN ₃ O ₅ S
276326	CONHSO ₂ Me	(S)4-F-PhCH ₂	F	H	C ₂₀ H ₂₂ F ₂ N ₄ O ₆ S ₂



276313: C18 H18 F N3 O5 S



276324: C31 H37 N5 O4



276325: C18 H25 N3 O5

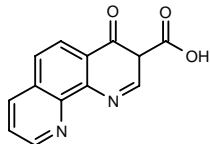
SOURCE – Merck & Co.

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276512

4-Oxo-3,4-dihydro[1,10]phenanthroline-3-carboxylic acid



C13 H8 N2 O3; Mol wt: 240.2172

ACTION – Prolyl 4-hydroxylase inhibitor useful for the treatment of disorders characterized by the proliferation of fibrotic tissue including rheumatoid arthritis, osteoarthritis, hepatic fibrosis, hepatic cirrhosis, pulmonary, renal and cardiac fibrosis, arteriosclerosis, tumor-associated fibrosis and the formation of scar tissue following injury or surgery. Compound proved effective following oral administration in several rat models of fibrotic disease, including myocardial fibrosis, restenosis, the formation of scar tissue in the brain following injury, kidney fibrosis and dermal wound healing. A representative compound from a series of phenanthroline derivatives.

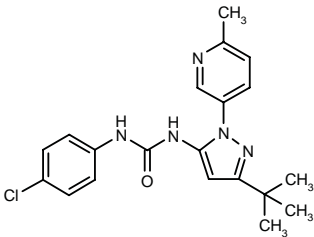
SOURCES – AstraZeneca; FibroGen.

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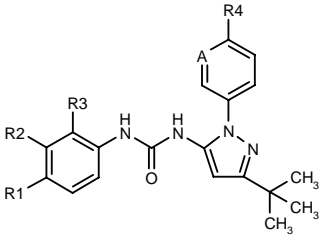
276687

N-[3-*tert*-Butyl-1-(6-methylpyridin-3-yl)-1*H*-pyrazol-5-yl]-*N'*-(4-chlorophenyl)urea



C20 H22 Cl N5 O; Mol wt: 383.8808

ACTION – Antiinflammatory agent that inhibits the release of proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF). Other specifically claimed aromatic heterocyclic compounds are:



Compound	R1	R2	R3	R4	A	Formula
276688	OMe	-CH=CHCH=CH-	Me	CH	CH	C ₂₈ H ₂₈ N ₄ O ₂
276689	F	H	H	Me	C(Me)	C ₂₂ H ₂₅ FN ₄ O
276690	H	H	F	Me	CH	C ₂₁ H ₂₃ FN ₄ O
276691	CN	-CH=CHCH=CH-	H	N	N	C ₂₄ H ₂₂ N ₆ O

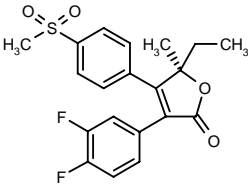
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Regan, J.R. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Aromatic heterocyclic cpds. as anti-inflammatory agents.* WO 9923091.

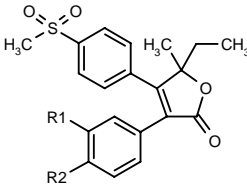
276692

3-(3,4-Difluorophenyl)-5(*R*)-ethyl-5-methyl-4-(4-methylsulfonylphenyl)furan-2(5*H*)-one



C20 H18 F2 O4 S; Mol wt: 392.4202

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated in CHO cells expressing the COX-2 enzyme and in COX-1-expressing U937 cell microsomes (IC₅₀ = 0.051 and 24.8 μM, respectively), as well as in the human whole blood assay (IC₅₀ = 1.55 and 76 μM for COX-2 and COX-1, respectively). Compound is reported to possess a shorter half-life (< 24 h) in rats than structurally related compounds and is thus expected to be devoid of side effects associated with an extended half-life. Other specifically claimed compounds within this series of diaryl-5-alkyl-5-methyl-2(5*H*)-furanones include the following:



Compound	R1	R2	Isomer	Formula
276693	H	F		C ₂₀ H ₁₉ FO ₄ S
276694	H	F	S	C ₂₀ H ₁₉ FO ₄ S
276695	H	F	R	C ₂₀ H ₁₉ FO ₄ S
276696	F	H		C ₂₀ H ₁₉ FO ₄ S
276697	F	F		C ₂₀ H ₁₈ F ₂ O ₄ S
276698	F	F	S	C ₂₀ H ₁₈ F ₂ O ₄ S

SOURCE – Merck Frosst.

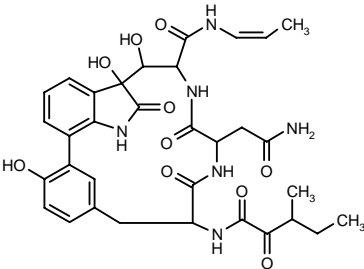
REFERENCES

1. Wang, Z. et al. (Merck Frosst Canada Inc.) *Diaryl-5-alkyl-5-methyl-2(5H)-furanones as selective cyclooxygenase-2 inhibitors.* WO 9923087.

TMC-95A

274602

15-Carbamoylmethyl-10,23-dihydroxy-18-(3-methyl-2-oxopentanamido)-9,14,17-trioxo-*N*-[1(*Z*)-propenyl]-8,13,16-triazatetracyclo[18.3.1.0^{2,7}.0^{6,10}]tetracos-1²⁴,2,4,6,20,22-hexaene-12-carboxamide



C33 H38 N6 O10; Mol wt: 678.6952

ACTION – Potent proteasome inhibitor isolated from *Apiospora montagnei* Sacc. (FERM P-16153), with an IC₅₀ value of 7.6 nM against chymotrypsin-like proteolytic activity of human monocyte-derived THP-1 proteasome, compared to IC₅₀ values for trypsin-like proteolytic activity and peptidyl glutamyl peptide hydrolytic activity of 160 and 95 nM, respectively. *In vivo*, it was effective in a rat model of adjuvant arthritis at 0.2 mg/kg/day s.c. x 21 days. Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Tanabe.

REFERENCES

1. Ohnuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Novel proteasome inhibitors*. JP 99029595.

IMMUNOMODULATING AGENTS

275339

Humanized anti-gp39 antibody

ACTION – Humanized antibody specific for human gp39 (also known as CD40 ligand or CD40L), particularly useful for the treatment of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, diabetes and systemic lupus erythematosus. It prevents CD40 signaling in B-cells, resulting in marked inhibition of T-cell activation and T-cell-mediated responses.

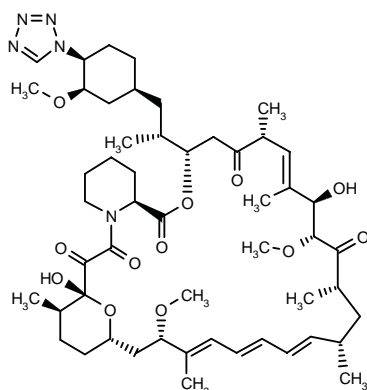
SOURCE – IDEC.

REFERENCES

1. Black, A. et al. (IDEC Pharmaceuticals Corp.) *Humanized antibodies to human gp39, compsns. containing and therapeutic use thereof*. WO 9912566.

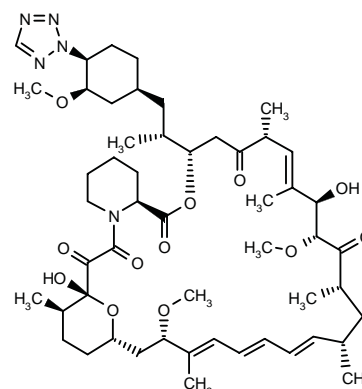
275709

(1*R*,9*S*,12*S*,15*R*,18*R*,19*R*,21*S*,23*S*,30*S*,32*S*,35*R*)-1,18-Dihydroxy-15,17,21,23,29,35-hexamethyl-12-[1(*R*)-methyl-2-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]ethyl]-19,30-dimethoxy-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone



C52 H79 N5 O12; Mol wt: 966.2191

ACTION – Immunosuppressant, a semisynthetic macrolide with minimal side effects due to its short half-life. Potentially useful for inhibiting restenosis and for the treatment of immune and autoimmune diseases, cancer, transplant rejection and fungal growth. Another compound from this series of tetrazole-containing rapamycin analogues is:



275710: C52 H79 N5 O12

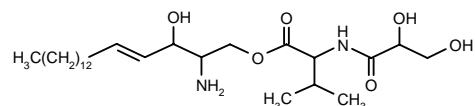
SOURCE – Abbott.

REFERENCES

1. Mollison, K.W. (Abbott Laboratories Inc.) *Tetrazole-containing rapamycin analogs with shortened half-lives*. WO 9915530.

275924

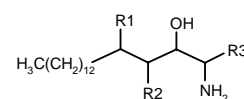
2-(2,3-Dihydroxypropionylamino)-3-methylbutyric acid 2-amino-3-hydroxyoctadec-4(*E*)-enyl ester



C26 H50 N2 O6; Mol wt: 486.6890

ACTION – Antifungal and immunosuppressive agent capable of regulating the function of sphingolipids; it gave an MIC value of 25 µg/ml against *Cryptococcus neoformans* TIMM 0354 and was active in the mixed lymphocyte reaction (MLR) using T-cells derived from murine spleen cells (IC₅₀ = 1.86 µg/ml). Other compounds from this series of sphingosine derivatives include the following:

(



Compound	R1	R2	R3	Formula
275925	H	H	CH2OCOCH(<i>i</i> -Pr)-NHCOCH(OH)CH2OH	C ₂₆ H ₅₂ N ₂ O ₆
275926	bond	bond	CH2OCOCH(OH)CH2OH	C ₂₁ H ₄₁ NO ₅
275927	bond	bond	CH2OCOCH(<i>i</i> -Pr)NH2	C ₂₃ H ₄₆ N ₂ O ₃
275928	H	H	CONHCH(Me)CONH-CH(<i>i</i> -Pr)CONHCH(CH2OH) ₂	C ₂₉ H ₅₈ N ₄ O ₆

SOURCE – Takara.

REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Sphingosine derivs. and medicinal compsn.* WO 9912890.

SOURCE – Tanabe.

REFERENCES

1. Ohnuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Novel proteasome inhibitors*. JP 99029595.

IMMUNOMODULATING AGENTS

275339

Humanized anti-gp39 antibody

ACTION – Humanized antibody specific for human gp39 (also known as CD40 ligand or CD40L), particularly useful for the treatment of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, diabetes and systemic lupus erythematosus. It prevents CD40 signaling in B-cells, resulting in marked inhibition of T-cell activation and T-cell-mediated responses.

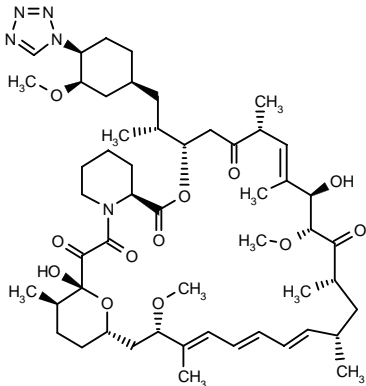
SOURCE – IDEC.

REFERENCES

1. Black, A. et al. (IDEC Pharmaceuticals Corp.) *Humanized antibodies to human gp39, compsns. containing and therapeutic use thereof*. WO 9912566.

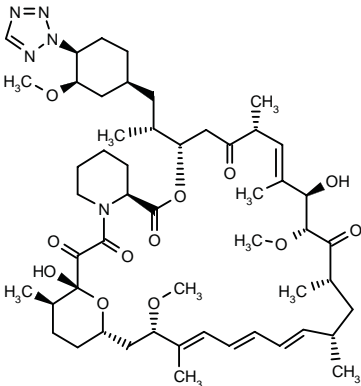
275709

(1*R*,9*S*,12*S*,15*R*,18*R*,19*R*,21*S*,23*S*,30*S*,32*S*,35*R*)-1,18-Dihydroxy-15,17,21,23,29,35-hexamethyl-12-[1(*R*)-methyl-2-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]ethyl]-19,30-dimethoxy-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone



C52 H79 N5 O12; Mol wt: 966.2191

ACTION – Immunosuppressant, a semisynthetic macrolide with minimal side effects due to its short half-life. Potentially useful for inhibiting restenosis and for the treatment of immune and autoimmune diseases, cancer, transplant rejection and fungal growth. Another compound from this series of tetrazole-containing rapamycin analogues is:



275710: C52 H79 N5 O12

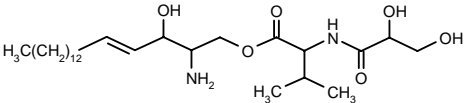
SOURCE – Abbott.

REFERENCES

1. Mollison, K.W. (Abbott Laboratories Inc.) *Tetrazole-containing rapamycin analogs with shortened half-lives*. WO 9915530.

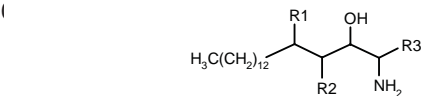
275924

2-(2,3-Dihydroxypropionylamino)-3-methylbutyric acid 2-amino-3-hydroxyoctadec-4(*E*)-enyl ester



C26 H50 N2 O6; Mol wt: 486.6890

ACTION – Antifungal and immunosuppressive agent capable of regulating the function of sphingolipids; it gave an MIC value of 25 µg/ml against *Cryptococcus neoformans* TIMM 0354 and was active in the mixed lymphocyte reaction (MLR) using T-cells derived from murine spleen cells (IC₅₀ = 1.86 µg/ml). Other compounds from this series of sphingosine derivatives include the following:



Compound	R1	R2	R3	Formula
275925	H	H	CH2OCOCH(<i>i</i> -Pr)-NHCOCH(OH)CH2OH	C ₂₆ H ₅₂ N ₂ O ₆
275926	bond		CH2OCOCH(OH)CH2OH	C ₂₁ H ₄₁ NO ₅
275927	bond		CH2OCOCH(<i>i</i> -Pr)NH2	C ₂₃ H ₄₆ N ₂ O ₃
275928	H	H	CONHCH(Me)CONH-CH(<i>i</i> -Pr)CONHCH(CH2OH)2	C ₂₉ H ₅₈ N ₄ O ₆

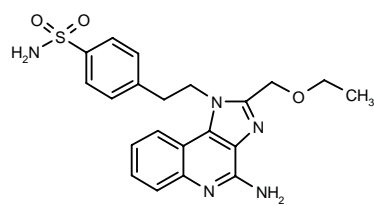
SOURCE – Takara.

REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Sphingosine derivs. and medicinal compsn.* WO 9912890.

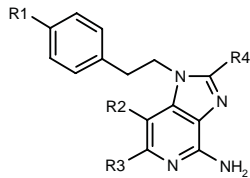
276245

4-[2-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]-quinolin-1-yl]ethyl]benzenesulfonamide



C21 H23 N5 O3 S; Mol wt: 425.5107

ACTION – Interferon-inducing compound shown to induce the production of interferon alfa in human peripheral blood monocytes at concentrations of 0.01-3 µg/ml. It is expected to be useful in the treatment of rheumatoid arthritis, warts, hepatitis B and C, and cancer. Other representative compounds from this series of imidazopyridines are:



Compound	R1	R2,R3	R4	Formula
276247	NHAc	-(CH=CHCH=CH-	H	C ₂₀ H ₁₉ N ₅ O
276249	CH2OH	-(CH2)4-	Et	C ₂₁ H ₂₆ N ₄ O
276251	CH(Me)NHAc	-(CH2)4-	H	C ₂₂ H ₂₇ N ₅ O
276252	NH2	-(CH2)4-	Me	C ₁₉ H ₂₃ N ₅

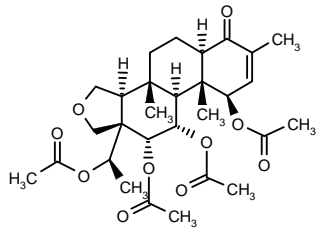
SOURCE – Hokuriku.

REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) 1-(Substd. aryl)alkyl-1*H*-imidazopyridine-4-amine derivs. JP 99080156.

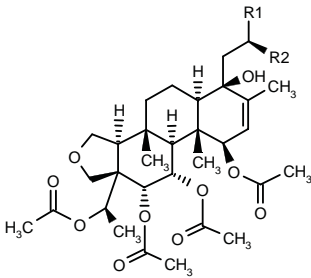
276378

[3a*S*-(3aα,3bβ,5aα,9β,9aβ,10α,11α,11aα)]-11a-[1(*R*)-Acetoxyethyl]-9,10,11-triacetoxy-3b,7,9a-trimethyl-3,3a,3b,4,5,5a,9,9a,9b,10,11,11a-dodecahydrophe-
nanthro[1,2-*c*]furan-6(1*H*)-one



C29 H40 O10; Mol wt: 548.6250

ACTION – Immunosuppressant with potential in the treatment of autoimmune diseases and organ transplant rejection. The compound acts as an inhibitor of the voltage-gated potassium channel Kv1.3 located on human T-lymphocytes and thereby inhibits T-cell activation. Other specifically claimed triterpenes include the following:



Compound	R1	R2	Formula
276379	vinyl	H	C ₃₃ H ₄₈ O ₁₀
276380	1-Naph	H	C ₄₁ H ₅₂ O ₁₀
276381	2,6-(MeO)2-Ph	H	C ₃₉ H ₅₄ O ₁₂
276382	2-Et-Ph	Me	C ₄₀ H ₅₆ O ₁₀

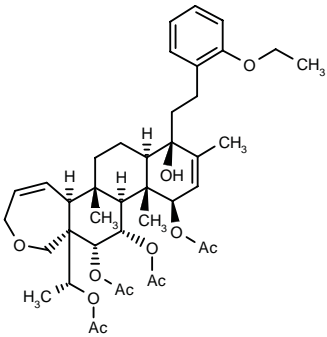
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) Furanyl, tetracyclic triterpene derivs. with immunosuppressant activity. WO 9920267.

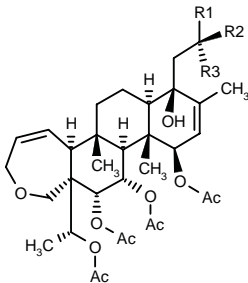
276383

(5a*S*,5b*S*,7a*R*,8*R*,11*R*,11a*R*,11b*S*,12*S*,13*R*)-13a-[1(*R*)-(Acetoxy)ethyl]-8-[2-(2-ethoxyphenyl)ethyl]-8-hydroxy-5b,9,11a-trimethyl-11,12,13-tris(acetoxy)-3,5a,5b,6,7,7a,8,11,11a,11b,12,13-dodecahydrophe-
nanthro[2,1-*c*]-oxepin



C41 H56 O11; Mol wt: 724.8824

ACTION – Immunosuppressant with potential in the treatment or prevention of organ transplant rejection and autoimmune diseases. Compound acts as an inhibitor of the voltage-dependent potassium channel Kv1.3 found on human T-lymphocytes and thereby inhibits T-cell activation. Other specifically claimed tetracyclic triterpene derivatives include the following:



Compound	R1	R2	R3	Formula
276384	2-(allyl-O)-Ph	H	H	C ₄₂ H ₅₆ O ₁₁
276385	vinyl	H	H	C ₃₈ H ₅₀ O ₁₀
276386	2-Me-Ph	H	H	C ₄₀ H ₅₄ O ₁₀
276387	Ph	Me	H	C ₄₀ H ₅₄ O ₁₀
276388	Ph	H	Me	C ₄₀ H ₅₄ O ₁₀
276389	2-MeO-Ph	-CH2-		C ₄₁ H ₅₄ O ₁₁
276390	2-Et-Ph	-CH2-		C ₄₂ H ₅₆ O ₁₀
276391	2-EtS-Ph	-CH2-		C ₄₂ H ₅₆ O ₁₀ S
276392	2-vinyl-Ph	-CH2-		C ₄₂ H ₅₄ O ₁₀

SOURCE – Merck & Co.

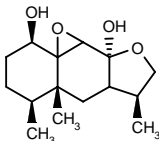
REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Tetracyclic triterpene derivs. with immunosuppressant activity.* WO 9920274.

EREMOPHYLLENE A

275427

(2*R*,5*S*,5*aR*,7*S*)-5,5*a*,7-Trimethylperhydrooxireno-[2',3':8*a*,1]naphtho[2,3-*b*]furan-2,9*a*-diol



C15 H24 O4; Mol wt: 268.3506

ACTION – Immunosuppressant and neovascularization inhibitor isolated from *Taxus cuspidata* OHHEIA strain (FERM P-16392), whose activity was demonstrated in the murine mixed lymphocyte reaction (MLR; IC₅₀ = 11.0 µg/ml) and also by inhibition of basic fibroblast growth factor (bFGF)-stimulated human umbilical vein endothelial cell (HUVEC) growth (IC₅₀ = 12.5 µg/ml).

SOURCE – Mercian.

REFERENCES

1. Sugawara, F. (Mercian Corp.) *Novel terpene cpd. eremophyllene A.* JP 99071377.

LYME DISEASE VACCINE

222452

Lyme disease vaccine (recombinant outer-surface protein A [OspA])

ACTION – Recombinant, noninfectious Lyme disease vaccine containing the outer-surface protein OspA of *Borrelia burgdorferi* that appears to act as follows: when infected ticks bite humans who have been vaccinated with this vaccine, the vaccine-induced antibodies are taken up by the tick and interact with the *B. burgdorferi* in the midgut of the tick, thereby preventing transmission of the organism to the host.

INDICATION – Prevention of Lyme disease in people 15-70 years of age who live or work in grassy or wooded areas where infected ticks are present.

PRESENTATION – Single-dose vials and prefilled syringes, 0.5 ml containing 30 µg lipoprotein OspA adsorbed onto 0.5 mg aluminum as aluminum hydroxide adjuvant.

PROPRIETARY NAME – LYMERix (US).

SOURCE – SmithKline Beecham.

REFERENCES

1. Goldenberg, M.M. *The immunogenicity and safety of a novel lyme disease vaccine, LYMERix.* P T 1998, 23(12): 614.

2. Steere, A.C. et al. *Vaccination against Lyme disease with recombinant Borrelia burgdorferi outer-surface lipoprotein A with adjuvant.* New Engl J Med 1998, 339(4): 209.

3. Telford, S.R. et al. *Efficacy of human lyme disease vaccine formulations in a mouse model.* J Infect Dis 1995, 171(5): 1368.

4. *Accelerated vaccination schedule effective for Lyme disease.* DailyDrugNews.com (Daily Essentials) 1999, June 10.

5. *Canadian launch for world's first Lyme disease vaccine.* DailyDrugNews.com (Daily Essentials) 1999, April 28.

6. *FDA advisory committee will meet to discuss Lyme disease and cholera vaccines.* DailyDrugNews.com (Daily Essentials) 1998, April 24.

7. *FDA approves first Lyme disease vaccine.* DailyDrugNews.com (Daily Essentials) 1998, Dec 22.

8. *First vaccine for Lyme disease now available from SB in the U.S..* DailyDrugNews.com (Daily Essentials) 1999, Jan 13.

9. *In development: New medicines for infectious diseases.* Pharmaceutical Research and Manufacturers of America 1994, December.

10. *SmithKline Beecham's Lyme disease vaccine recommended for FDA approval.* DailyDrugNews.com (Daily Essentials) 1998, May 27.

11. *SmithKline Beecham: Annual report 1998/Q1 report 1999.* DailyDrugNews.com (Daily Essentials) 1999, April 27.

12. SmithKline Beecham Annual Report 1995

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

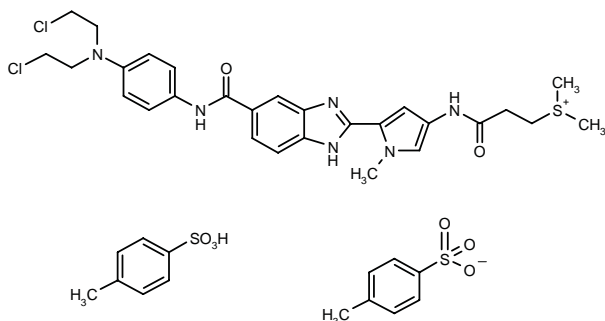
MS-247*

274485

256607 (as monotosylate)

255726 (as mesylate)

S-[2-[N-[5-[N-[4-[Bis(2-chloroethyl)amino]-phenyl]carbamoyl]-1*H*-benzimidazol-2-yl]-1-methylpyrrol-3-yl]carbamoyl]ethyl]-S,S-dimethylsulfonium bis(4-methylbenzenesulfonate)



C₂₈ H₃₃ Cl₂ N₆ O₂ S . C₇ H₈ O₃ S . C₇ H₇ O₃ S; Mol wt: 931.9792

ACTION – Antineoplastic agent, a DNA minor groove binder with significant cytotoxicity against several murine and human tumor cell lines. Compound exhibited strong activity superior to doxorubicin and cisplatin against 17 human tumor xenografts in mice including colon, lung, stomach, breast and ovarian tumor xenografts. In particular, compound showed marked inhibition of tumor growth in mice bearing lung NCI-H23 (T/C = 4%), DMS114 (T/C = 19%) and DMS273 (T/C = 2%). Compound was also active against paclitaxel- (HCT15) and CPT-11-resistant (A549, HBC-4 and SK-OV-3) cancers. It was selected as a candidate for clinical evaluation.

SOURCE – Mitsui Pharmaceuticals.

REFERENCES

1. Matsunaga, A. et al. (Mitsui Chemicals, Inc.) *Pyrrolylbenzimidazole derivs.* EP 776891, JP 97208580, JP 97208581, US 5808087.
2. Matsunaga, A. et al. *A novel DNA minor groove binder MS-247: Design, synthesis and antitumor activity against human cancer xenografts.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2005.

*Identified compound **255726** and **256607** (see **255726**) Drug Data Report 1998, 020(01): 0081.

ANTIMETABOLITES

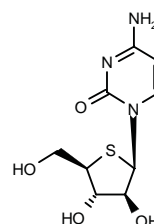
4'-Thio-ara-C

274478

4'-Thio-β-D-arabinofuranosylcytosine

4-Amino-1-(4-thio-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone

1-(4-Thio-β-D-arabinofuranosyl)cytosine



C₉ H₁₃ N₃ O₄ S; Mol wt: 259.2847

ACTION – Antineoplastic agent, a nucleoside analogue with significant cytotoxic activity against various human tumor cell lines such as renal CAKI-1, non-small cell lung NCI-H23, colon DLD-1, melanoma SK-MEL-28 and LOX IMVI, CNS SNB-7, prostate PC-3 and breast ZR-75-1 tumor cells, with ID₅₀ values ranging from 1 to 10 μM and being about 5-fold less potent than ara-C. Compound exhibited excellent *in vivo* activity against a variety of human cancer cell lines implanted in mice. In particular, the agent was curative against colon HCT-116 and SW-620 and renal CAKI-1 tumors, against which ara-C was minimally active. It is considered a candidate for clinical evaluation.

SOURCE – Southern Research Institute, Birmingham, AL (US).

REFERENCES

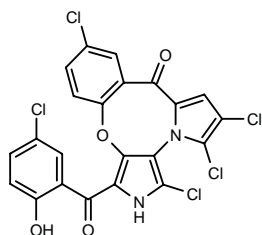
1. Ottoni, N. and Whistler, R.L. *Preparation and antitumor activity of 4'-thio analogs of 2,2'-anhydro-1-β-D-arabinofuranosylcytosine.* J Med Chem 1974, 17(5): 535.
2. Parker, W.B. et al. *Metabolism of 4'-thio-arabinofuranosyl cytosine (T-araC) in CEM cells.* Proc Amer Assoc Cancer Res 1999, 40: Abst 1973.
3. Waud, W.R. et al. *Preclinical antitumor activity of 4'-thio-beta-D-arabinofuranosylcytosine (4'-thio-ara-C).* Proc Amer Assoc Cancer Res 1999, 40: Abst 1972.
4. Whistler, R.L. et al. *4-Thio-D-arabinofuranosylpyrimidine nucleosides.* J Org Chem 1971, 36(1): 108.

ANTIBIOTICS AND ALKALOIDS

BE-55051

275428

1,7,11,12-Tetrachloro-3-(5-chloro-2-hydroxybenzoyl)-2*H*,9*H*-dipyrrolo[3,4-*b*:1,2-*d'*][1,4]benzoxazocin-9-one



C22 H9 Cl5 N2 O4; Mol wt: 542.5881

ACTION – Antineoplastic agent isolated from a culture of the microorganism *Streptomyces* sp. A55051 (FERM P-16028), with *in vitro* cytotoxicity against murine leukemia P388 (IC₅₀ = 0.61 µg/ml), murine colon cancer 26 (IC₅₀ = 0.27 µg/ml), human colon cancer DLD-1 (IC₅₀ = 0.29 µg/ml), human lung cancer PC-13 (IC₅₀ = 0.59 µg/ml) and human gastric cancer MKN-45 cells (IC₅₀ = 0.31 µg/ml).

SOURCE – Banyu.

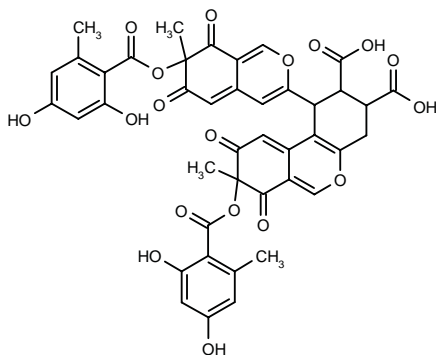
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DIAZAPHILONIC ACID

275297

8-(2,4-Dihydroxy-6-methylbenzoyloxy)-1-[7-(2,4-dihydroxy-6-methylbenzoyloxy)-7-methyl-6,8-dioxo-7,8-dihydro-6*H*-2-benzopyran-3-yl]-8-methyl-7,9-dioxo-2,3,4,7,8,9-hexahydro-1*H*-dibenzo[*b*,*d*]pyran-2,3-dicarboxylic acid



C42 H32 O18; Mol wt: 824.6968

Yellow powder, $[\alpha]_D^{25}$ –371° (c 0.5, MeOH).

ACTION – Azaphilone-type microbial metabolite produced by *Talaromyces flavus* PF1195, proven to inhibit telomerase activity in human leukemia MT1 cells (almost complete inhibition at 50 µM). Compound also inhibited DNA amplification by polymerase chain reaction (PCR) with Tth DNA polymerase, giving an IC₅₀ value of 2.6 µg/ml. Compound did not show antimicrobial activity against Gram-positive or Gram-negative bacteria or yeasts.

SOURCE – Meiji Seika.

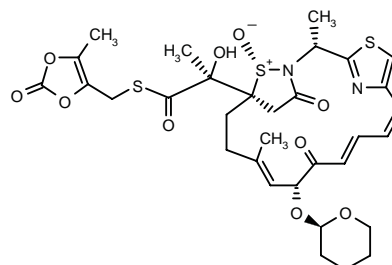
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1. Tabata, Y. et al. *Diazaphilonic acid, a new azaphilone with telomerase inhibitory activity*. J Antibiot 1999, 52(4): 412.

KF-22678

255759

(α *R*,2*R*,7*Z*,9*E*,12*R*,13*E*,17*R*,20*S*)- α -Hydroxy- α ,2,14-trimethyl-11,19-dioxo-12-[tetrahydropyran-2(*R*)-yloxy]-4,20-dithia-1,21-diazatricyclo[15.2.1.1^{3,6}]heneicosa-3(21),5,7,9,13-pentanene-17-ethanetic acid 20-oxide *S*-(5-methyl-2-oxo-1,3-dioxol-4-ylmethyl) ester



C32 H38 N2 O10 S3; Mol wt: 706.8542

ACTION – Antineoplastic agent, a derivative of the antibiotic leinamycin with potent antiproliferative activity against HeLa S3 cells (IC₅₀ = 0.67 nM). *In vivo*, compound showed antitumor activity in mice inoculated with murine sarcoma 180 cells (T/C = 0.26 at the optimal dose of 8.0 mg/kg i.v.), as well as against human tumor xenografts such as lung, liver, ovarian, prostatic and colon carcinomas. It has been selected for further evaluation.

SOURCE – Kyowa Hakko.

REFERENCES

1. Kanda, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *DC107 derivs*. EP 786462, WO 9700260.

2. Ashizawa, T. et al. *Antitumor activity of KF22678, a novel DC107 derivative (I)*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-002.

3. Kanda, Y. et al. *Synthesis and antitumor activity of novel thioester derivatives of leinamycin*. J Med Chem 1999, 42(8): 1330.

NOSCAPINE

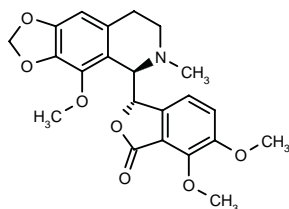
Rec INN; BAN; USAN

New use

274460

6,7-Dimethoxy-3(*S*)-[4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5(*R*)-yl]isobenzofuran-1(*3H*)-one

NSC-5366



C22 H23 N O7; Mol wt: 413.4237

ACTION – Antineoplastic agent, an alkaloid extracted from opium that has been used as an antitussive since 1963. Compound has now been found to act by binding to tubulin subunits, altering tubulin assembly, arresting mammalian cells in mitosis and causing apoptosis in cycling cells. It showed antiproliferative effects in HeLa cells and thymocytes, as well as in human breast (MCF-7) and bladder (Renal 1983) cancer cells (IC_{50} = 25, 10, 42.3 and 39.1 μ M, respectively), and human ovarian cancer MA148 and OC494 cells including paclitaxel-resistant cells. At a dose of 120 mg/kg/day i.p. for 3 weeks, it inhibited the growth of human breast MCF-7 tumors xenografted in nude mice by 80%, and at a dose of 240 mg/kg/day i.p. for 4 weeks it significantly inhibited the growth of ovarian cancer, with complete responses in almost half of the animals. Compound exhibited good oral absorption and low general toxicity in mice.

SOURCE – Emory University, Atlanta, GA (US).

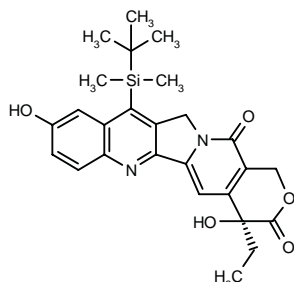
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1. Ghosh, K. et al. *Noscapine, a new antitumor agent in the treatment of ovarian cancer*. Proc Amer Assoc Cancer Res 1999, 40: Abst 1368.
2. Ye, K. et al. *Opium alkaloid noscapine is an antitumor agent that arrests metaphase and induces apoptosis in dividing cells*. Proc Natl Acad Sci USA 1998, 95(4): 1601.

DNA-INTERCALATING DRUGS

274543

11-(*tert*-Butyldimethylsilyl)-4(*S*)-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione



C26 H30 N2 O5 Si; Mol wt: 478.6180

ACTION – Antineoplastic agent, an analogue of camptothecin that is 25 times more lipophilic and more stable in human blood ($t_{1/2}$ = 130 min) than camptothecin. Compound showed excellent activity in a cell-free topoisomerase I assay. Liposomal formulations of the compound are currently being evaluated for antitumor activity *in vivo* in human tumor xenograft models in mice.

SOURCES – National Cancer Institute, Bethesda, MD (US); Stehlin Foundation for Cancer Research, Houston, TX (US).

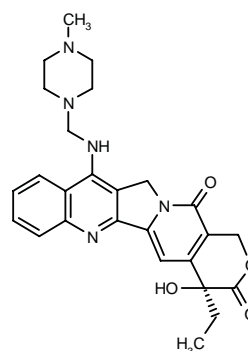
REFERENCES

1. Burke, T.G. et al. *Development and evaluation of a liposomal formulation of highly lipophilic 7-*tert*-butyldimethylsilyl-10-hydroxy-camptothecin*. Proc Amer Assoc Cancer Res 1999, 40: Abst 752.

CT-17

274542

4(*S*)-Ethyl-4-hydroxy-11-(4-methylpiperazin-1-ylmethylamino)-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione



C26 H29 N5 O4; Mol wt: 475.5461

ACTION – Antineoplastic agent, a highly water-soluble analogue of camptothecin that inhibits topoisomerase I activity to a lesser extent as compared to the parent compound but whose physicochemical properties enable it to be loaded into liposomal particles, resulting in liposomal formulations with higher stability in human plasma than camptothecin.

SOURCES – National Cancer Institute, Bethesda, MD (US); Stehlin Foundation for Cancer Research, Houston, TX (US).

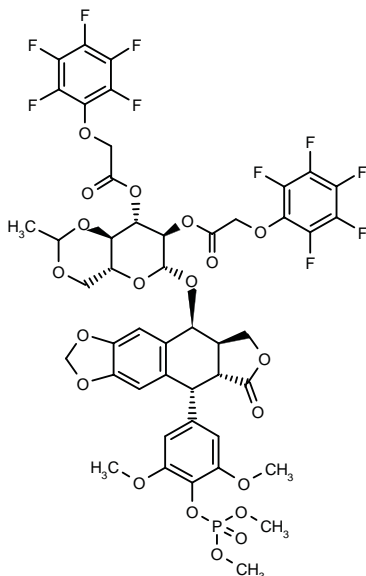
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1. Demir, A.S. et al. *Synthetic design, physical and biological characterization of a novel water-soluble camptothecin analog containing a polyamine functionality at position 7*. Proc Amer Assoc Cancer Res 1999, 40: Abst 715.

F-11782

274522

(5*R*,5*aR*,8*aR*,9*S*)-5-[3,5-Dimethoxy-4-(dimethoxyphosphoryloxy)phenyl]-9-[4,6-*O*-ethylidene-2,3-*O*-bis(pentafluorophenoxymethylcarbonyl)-β-D-glucopyranosyloxy]-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]-naphtho[2,3-*d*][1,3]dioxol-6-one



C47 H39 F10 O20 P; Mol wt: 1144.7590

ACTION – Antineoplastic lipophilic epipodophyllotoxin derivative, a dual inhibitor of topoisomerases (Topo) I and II, with strong activity in relaxation and decatenation assays ($EC_{50} = 3.2$ and $0.76 \mu\text{M}$, respectively), as well as DNA repair. Compound did not show DNA-intercalating properties and did not stabilize cleavable complexes induced by Topo I or II; it appeared to interact directly with Topo I and II, preventing their binding to DNA via a mechanism not associated with a direct DNA interaction. The *in vitro* cytotoxic profile of compound is different from other Topo inhibitors, indicating a distinct mechanism of action. F-11782 exhibited *in vitro* cytotoxic effects, blocking murine leukemia P388 cells in the G2/M phase of the cell cycle and inducing apoptosis. *In vivo*, compound exhibited more potent antitumor activity than etoposide, prolonging survival and inhibiting the growth of murine leukemia P388, murine melanoma B16 and human breast MX-1 tumor xenografts in mice.

SOURCE – Pierre Fabre.

REFERENCES

1. Imbert, T. et al. (Pierre Fabre Médicament) *Water-soluble epipodophyllotoxin derivs., preparation method therefor, and use thereof as a drug and for treating cancer*. FR 2725990, JP 98507462, WO 9612727.
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3. Etievant, C. et al. *In vitro cytotoxic effects of F 11782, a novel catalytic dual inhibitor of topoisomerases I and II*. Proc Amer Assoc Cancer Res 1999, 40: Abst 759.
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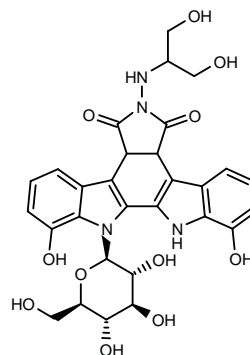
6. Perrin, D. et al. *Biological characterization of the in vitro activities of F 11782, a novel catalytic dual inhibitor of topoisomerases I and II*. Proc Amer Assoc Cancer Res 1999, 40: Abst 756.

7. van Hille, B. et al. *F11782, a novel epipodophylloid, functions as a dual inhibitor of topoisomerases I and II*. Proc Amer Assoc Cancer Res 1999, 40: Abst 762.

J-109404

276066

1,11-Dihydroxy-12-(β-D-glucopyranosyl)-6-[2-hydroxy-1-(hydroxymethyl)ethylamino]-12,13-dihydro-4*cH*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*,7*aH*)-dione



C29 H30 N4 O11; Mol wt: 610.5730

ACTION – Antineoplastic agent, an inhibitor of topoisomerase I ($EC_{50} = 0.58 \mu\text{M}$ in a topoisomerase I-mediated DNA cleavage assay) with more than 100-fold selectivity over topoisomerase II, epidermal growth factor (EGF) receptor kinase and protein kinase C (PKC). Compound showed *in vitro* cytotoxicity against murine leukemia P388/S and human stomach cancer MKN-45 cells ($IC_{50} = 0.017$ and $0.13 \mu\text{M}$, respectively). *In vivo*, it inhibited the growth of MKN-45 xenografts implanted s.c. into nude mice, with a GID_{75} (75% growth inhibition dose) of 78 mg/m^2 i.v. given 5 times/week for 2 weeks. It was as active as NB-506 *in vitro*, but showed better anticancer activity *in vivo* and a higher safety margin.

SOURCES – Banyu; Merck & Co.

REFERENCES

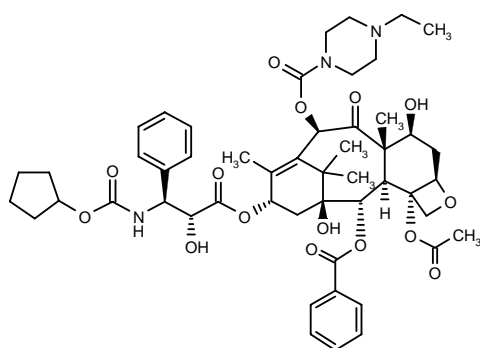
1. Ohkubo, M. et al. *Synthesis and biological activities of topoisomerase I inhibitors, 6-N-amino analogues of NB-506*. Bioorg Med Chem Lett 1999, 9(9): 1219.

ANTIMITOTIC DRUGS

276089

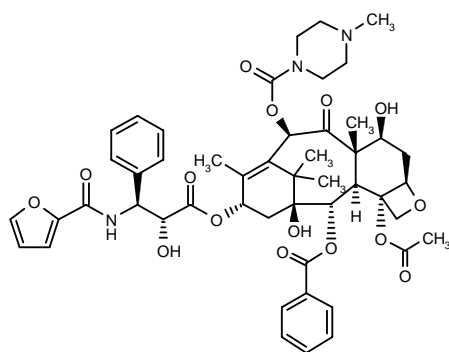
[2a*R*,4*S*,4a*S*,6*R*,9*S*(2*R*,3*S*),11*S*,12*S*,12a*R*,12b*S*]-12b-Acetoxy-9-[3-(cyclopentyloxycarbonylamino)-2-hydroxy-3-phenylpropionyloxy]-6-(4-ethylpiperazin-1-ylcarbonyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one

3'-*N*-Cyclopentyloxycarbonyl-10-*O*-(4-ethylpiperazin-1-ylcarbonyl)paclitaxel



C51 H65 N3 O15; Mol wt: 960.0805

ACTION – Antineoplastic agent, a taxane derivative with comparable antitumor activity to paclitaxel against KB cells (GI_{50} = 1.4 ng/ml vs. 1.3 ng/ml for paclitaxel) and highly improved water solubility (2000 μ g/ml vs. 0.4 μ g/ml for paclitaxel). Another taxane derivative is:



276090: C49 H57 N3 O15

SOURCE – Yakult Honsha.

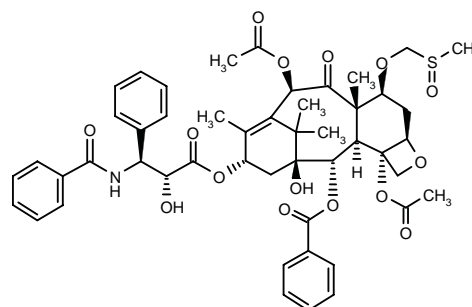
REFERENCES

1. Abe, A. et al. (Yakult Honsha Co., Ltd.) *New taxane derivs.* JP 99092468, WO 9914209.

276679

[2a*R*,4*S*,4a*S*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12a*R*,12b*S*]-6,12b-Diacetoxy-9-(3-benzamido-2-hydroxypropionyloxy)-12-benzoyloxy-11-hydroxy-4a,8,13,13-tetramethyl-4-(methylsulfinylmethoxy)-7,11-methano-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-cyclodeca[3,4]-benz[1,2-*b*]oxet-5-one

7-*O*-(Methylsulfinylmethyl)paclitaxel



C49 H55 N O15 S; Mol wt: 930.0315

ACTION – Antineoplastic agent, a paclitaxel derivative that was slightly less active than paclitaxel against human colon tumor HCT 116 cells (IC_{50} = 13 nM vs. 4.9-5.9 nM). Mice bearing Madison 109 lung carcinomas treated at doses of 15 and 25 mg/kg i.v. showed increased survival and tumor growth delay compared to controls.

SOURCE – Bristol-Myers Squibb.

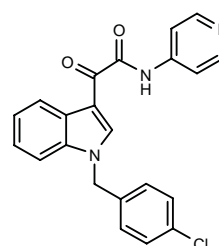
REFERENCES

1. Golik, J. and Vyas, D.M. (Bristol-Myers Squibb Co.) *7-Methylthiooxomethyl and 7-methylthiodioxomethyl paclitaxels.* US 5902822.

D-24851

274466

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-oxo-*N*-(4-pyridyl)-acetamide



C22 H16 Cl N3 O2; Mol wt: 389.8404

ACTION – Antineoplastic agent, a tubulin-interacting compound with *in vitro* cytotoxic activity against several tumor cell lines including epidermoid carcinoma KB, murine leukemia L1210, breast carcinoma MCF-7, prostate carcinoma LNCAP, ovarian carcinoma SK-OV-3 and lung carcinoma HT-29 cell lines (EC_{50} = 40-80 nM). Cytotoxic activity was also observed against brain tumor U-118 MG, U-87 MG and U-373 MG cell lines (EC_{50} = 0.1-1 μ M). The cytotoxic activity of compound was due to cell cycle arrest in the G2/M phase through microtubule destabilization. Compound showed broad-spectrum antitumor activity *in vivo* superior to vincristine or paclitaxel; in particular, compound (20 mg/kg x 8 p.o.) exhibited curative activity in 90% of sarcoma AH13-bearing rats without treatment-associated side effects.

SOURCE – Asta Medica.

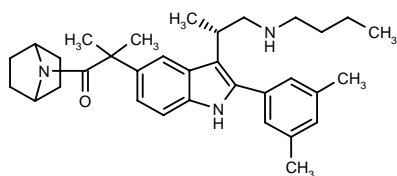
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2. Bacher, G. et al. *D-24851, a small molecule, destabilizes microtubules*. Proc Amer Assoc Cancer Res 1999, 40: Abst 1893.
3. Nickel, B. et al. *D-24851, a novel tubulin-interacting agent, preclinical antineoplastic effects*. Proc Amer Assoc Cancer Res 1999, 40: Abst 4110.

HORMONAL AGENTS

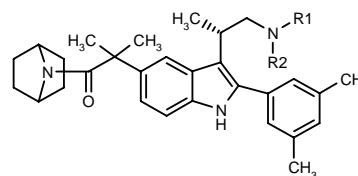
276462

1-(7-Azabicyclo[2.2.1]hept-7-yl)-2-[3-[2-(butylamino)-1(*S*)-methylethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-2-methyl-1-propanone



C33 H45 N3 O; Mol wt: 499.7385

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-related and other disorders. Specifically, its use is claimed in the treatment of sex hormone-dependent cancer, endometriosis, polycystic ovarian disease, precocious puberty, lupus erythematosus, irritable bowel syndrome, premenstrual syndrome, hirsutism, sleep disorders such as sleep apnea and short stature or growth hormone deficiency, as well as for preventing pregnancy. Other representative compounds are:



Compound	R1	R2	Formula
276464	-CH2CH2CH(OH)CH2CH2-		C ₃₄ H ₄₅ N ₃ O ₂
276465	CO ₂ Et	H	C ₃₂ H ₄₁ N ₃ O ₃
276466	COEt	H	C ₃₂ H ₄₁ N ₃ O ₂
276467	4-morpholinyl-CH2CH2	H	C ₃₅ H ₄₈ N ₄ O ₂

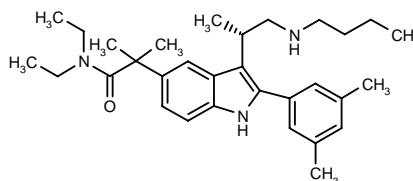
SOURCE – Merck & Co.

REFERENCES

1. Chu, L. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9921553.

276470

2-[3-[2-(Butylamino)-1(*S*)-methylethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-5-yl]-*N,N*-diethyl-2-methylpropanamide



C31 H45 N3 O; Mol wt: 475.7165

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-related and other disorders. Specifically, its use is claimed in the treatment of sex hormone-dependent cancer, endometriosis, polycystic ovarian disease, precocious puberty, lupus erythematosus, irritable bowel syndrome, premenstrual syndrome, hirsutism, sleep disorders such as sleep apnea and short stature or growth hormone deficiency, as well as for preventing pregnancy.

SOURCE – Merck & Co.

REFERENCES

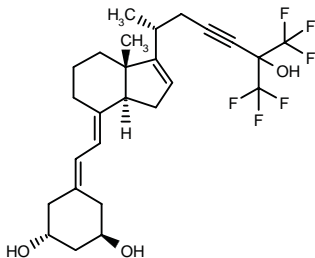
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RO-25-6760*

231343

26,26,26,27,27,27-Hexafluoro-1 α ,25-dihydroxy-16,17,23,23,24,24-hexadehydro-19-norvitamin D₃

(1 α ,3 β ,7*E*)-26,26,26,27,27,27-Hexafluoro-19-nor-9,10-secocholesta-5,7,16-trien-23-yne-1,3,25-triol



C26 H32 F6 O3; Mol wt: 506.5340

ACTION – Antineoplastic agent, a synthetic vitamin D₃ analogue with antiproliferative activity against human colon cancer HT-29 (0.1 nM-1 μ M), human breast cancer MCF-7 and SK-BR-3 (ED₅₀ = 0.01 nM) and human prostate cancer cells (LNCaP, PC-3 and DU-145). Compound appears to act by inducing G0/G1 cell cycle arrest and apoptosis. It was effective in mice bearing human colon cancer HT-29 xenografts, significantly inhibiting tumor growth at doses of 0.1 and 0.2 μ g i.p. 3 times weekly, without causing hypercalcemia or other side effects.

SOURCE – Roche.

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1. Baggiolini, B.J. et al. (F. Hoffmann-La Roche AG) *Vitamin D₃ fluorinated analogs*. US 5451574, US 5753638.

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3. Bollag, W. et al. (F. Hoffmann-La Roche AG) *Pharmaceutical compsns. containing 9-cis- o 13-cis-retinoic acid or acitretin and a vitamin D deriv*. EP 579915.

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7. Campbell, M.J. et al. *Retinoids and vitamin D₃ analogs synergistically inhibit clonal growth of prostate cancer cells*. Proc Amer Assoc Cancer Res 1996, 37: Abst 1687.

8. Campbell, M.J. et al. *Synergistic inhibition of prostate cancer cell lines by a 19-nor hexafluoride vitamin D₃ analogue and antiactivator protein 1 retinoid*. Br J Cancer 1999, 79(1): 101.

9. Chen, S. et al. *Suppression of ANP gene transcription by liganded vitamin D receptor: Involvement of specific receptor domains*. Hypertension 1998, 31(6): 1338.

10. Evans, S.R.T. et al. *Growth inhibitory effects of 1,25-dihydroxyvitamin D₃ and its synthetic analogue, 1 α ,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-19-nor-cholecalciferol (Ro 25-6760), on a human colon cancer xenograft*. Clin Cancer Res 1998, 4(11): 2869.

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12. Fioravanti, L. et al. *Synthetic analogs of vitamin D3 have inhibitory effects on breast cancer cell lines*. Anticancer Res 1998, 18(3A): 1703.

13. Hedlund, T.E. et al. *Three synthetic vitamin D analogues induce prostate-specific acid phosphatase and prostate-specific antigen while inhibiting the growth of human prostate cancer cells in a vitamin D receptor-dependent fashion*. Clin Cancer Res 1997, 3(8): 1331.

14. Koike, M. et al. *19-nor-Hexafluoride analogs of vitamin D₃: A novel class of potent inhibitors of proliferation and induction of p27/Kip1 in human breast cancer cell lines*. Proc Amer Assoc Cancer Res 1997, 38: Abst 579.

15. Koike, M. et al. *19-nor-hexafluoride analogue of vitamin D₃: A novel class of potent inhibitors of proliferation of human breast cell lines*. Cancer Res 1997, 57(20): 4545.

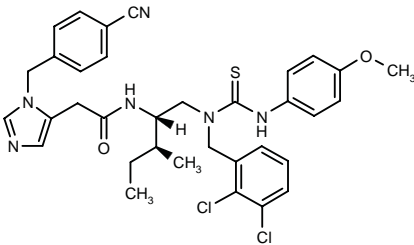
16. Pakkala, S. et al. *Vitamin D₃ analogs: Effect on leukemic clonal growth and differentiation, and on serum calcium levels*. Leuk Res 1995, 19(1): 65.

*Identified compound 231343 Drug Data Report 1996, 018(04): 0353.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

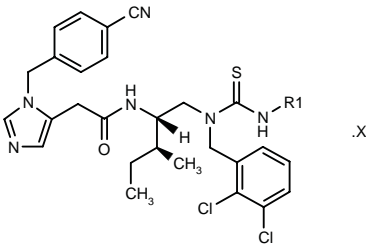
275358

N-[2(*S*)-[2-[1-(4-Cyanobenzyl)imidazol-5-yl]acetamido]-3(*S*)-methylpentyl]-*N*-(2,3-dichlorobenzyl)-*N'*-(4-methoxyphenyl)thiourea



C34 H36 Cl2 N6 O2 S; Mol wt: 663.6704

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC₅₀ = 26.7 nM) shown to potently inhibit K-ras-transformed cell growth *in vitro* (IC₅₀ = 0.045 μ M), as well as K-ras processing in NIH3T3 cells transfected with human K-ras4B (80-100% inhibition at 10 μ M). A representative compound from a series of thiourea derivatives, wherein the following are also included:



Compound	R1	X	Formula
275359	cyclohexyl		C ₃₃ H ₄₀ Cl ₂ N ₆ OS
275360	6-MeO-3-Pyr		C ₃₃ H ₃₅ Cl ₂ N ₇ O ₂ S
275361	4-MeO-Ph	HCl	C ₃₄ H ₃₆ Cl ₂ N ₆ O ₂ S.HCl
275362	cyclohexyl	HCl	C ₃₃ H ₄₀ Cl ₂ N ₆ OS.HCl

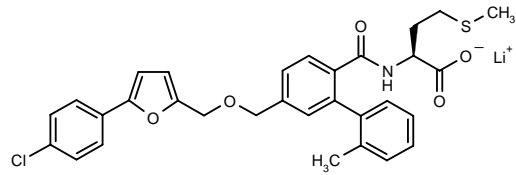
SOURCE – Yuhan.

REFERENCES

1. Lee, B.Y. et al. (Yuhan Corp.) *Thiourea derivs. or non-toxic salts thereof for inhibiting ras-transformed cell growth*. WO 9912912.

275548

N-[5-[5-(4-Chlorophenyl)-2-furylmethoxymethyl]-2'-methylbiphenyl-2-ylcarbonyl]-L-methionine lithium salt



C31 H29 Cl Li N O5 S; Mol wt: 570.0321

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC₅₀ = 0.7 nM) and of the farnesylation of the oncogene protein Ras (EC₅₀ = 0.1 μM in a whole-cell assay). Compound showed a favorable pharmacokinetic profile, with an oral bioavailability of 30% in rats and 21% in dogs.

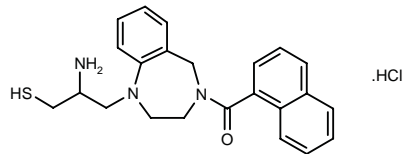
SOURCES – Abbott; University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

1. Sebtì, S.M. et al. (University of Pittsburgh) *Inhibitors of protein isoprenyl transferases*. WO 9850029, WO 9850030, WO 9850031.
2. Augeri, D.J. et al. *Potent and orally bioavailable noncysteine-containing inhibitors of protein farnesyltransferase*. Bioorg Med Chem Lett 1999, 9(8): 1069.

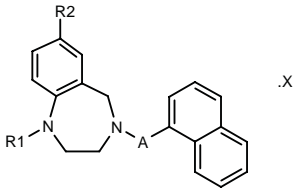
276102

1-[1-(2-Amino-3-sulfanylpropyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-4-yl]-1-(naphthalen-1-yl)methanone hydrochloride

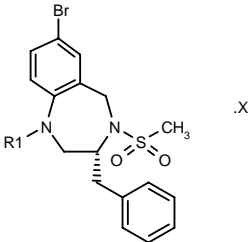


C23 H25 N3 O S . HCl; Mol wt: 427.9974

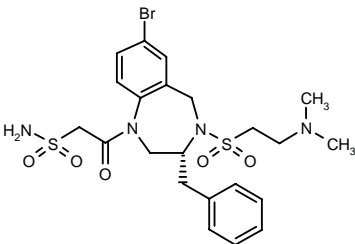
ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Within this series of benzodiazepine derivatives, the following are also specifically claimed:



Compound	R1	R2	A	X	Formula
276103	CH2CH(NH2)CH2SH	Ph	-CO-	HCl	C ₂₉ H ₂₉ N ₃ O ₃ .HCl
276104	3-Pyr-NHCO	H	-SO2-		C ₂₅ H ₂₂ N ₂ O ₃ S
276107	2-thienyl-CH2	H	-CO-		C ₂₅ H ₂₂ N ₂ O ₃ S
276109	3-Pyr-CH2	Ph	-CO-	HCl	C ₃₂ H ₂₇ N ₃ O ₃ .HCl
276110	3-thienyl-CH2	H	-CO-		C ₂₅ H ₂₂ N ₂ O ₃ S
276111	3-OH-2-oxo-1,2-dihydro-1-Pyr-CH2CH2	H	-CO-	2HCl	C ₂₇ H ₂₅ N ₃ O ₃ .2HCl
276112	3-OH-2-oxo-1,2-dihydro-1-Pyr-CH2CH2	Ph	-CO-	2HCl	C ₃₃ H ₃₉ N ₃ O ₃ .2HCl
276113	5-oxo-2-pyrrolidinyl-CO	Ph	-CO-		C ₃₁ H ₂₇ N ₃ O ₃
276114	2-Pyr-NH(CH2)3	Ph	-CO-	2HCl	C ₃₄ H ₃₂ N ₄ O ₃ .2HCl
276115	3-Pyr-NH(CH2)3	Ph	-CO-	2HCl	C ₃₄ H ₃₂ N ₄ O ₃ .2HCl
276116	3-pyrazolyl-NH(CH2)3	Ph	-CO-	2HCl	C ₃₂ H ₃₁ N ₅ O ₃ .2HCl
276117	2-pyrimidinyl-NH(CH2)3	Ph	-CO-	2HCl	C ₃₃ H ₃₂ N ₅ O ₃ .2HCl



Compound	R1	X	Formula
276105	2-oxo-1-pyrrolidinyl-CH2CO	CF3CO2H	C ₂₃ H ₂₆ BrN ₃ O ₄ S .C ₂ HF ₃ O ₂
276118	3-Pyr-CH2	HCl	C ₂₃ H ₂₄ BrN ₃ O ₂ S.HCl
276119	1-oxido-3-Pyr-CH2	HCl	C ₂₃ H ₂₄ BrN ₃ O ₃ S.HCl
276120	2-Pyr-CH2	HCl	C ₂₃ H ₂₄ BrN ₃ O ₂ S.HCl
276121	4-Pyr-CH2	HCl	C ₂₃ H ₂₄ BrN ₃ O ₂ S.HCl
276122	CH2CONHOH	HCl	C ₁₉ H ₂₂ BrN ₃ O ₄ S.HCl



276106: C22 H29 Br N4 O5 S2

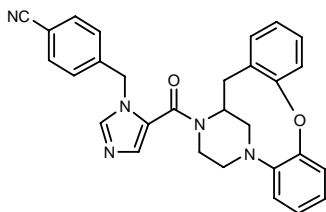
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Ding, C.Z. et al. (Bristol-Myers Squibb Co.) *Inhibitors of farnesyl protein transferase*. WO 9918951.

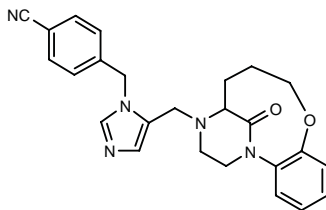
276168

4-[5-(5,6,7,8,9,10-Hexahydro-5,9-methanodibenzo-[b,*j*][1,4,7]oxadiazacycloundecin-8-ylcarbonyl)-1*H*-imidazol-1-ylmethyl]benzonitrile

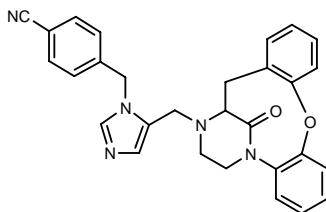


C29 H25 N5 O2; Mol wt: 475.5495

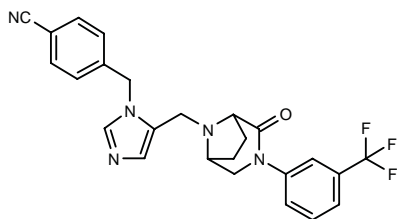
ACTION – Protein farnesyltransferase inhibitor potentially useful in the treatment and/or prevention of cancer, benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related infections, restenosis and polycystic kidney disease. Other specifically claimed conformationally constrained, non-thiol-containing compounds include the following:



276169: C25 H25 N5 O2



276170: C29 H25 N5 O2



276171: C25 H22 F3 N5 O

SOURCE – Merck & Co.

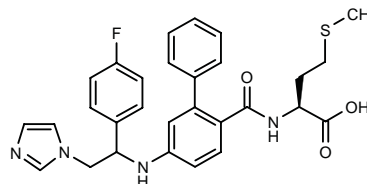
REFERENCES

1. Bergman, J.M. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9920609.

276173

2(*S*)-[5-[1-(4-Fluorophenyl)-2-(1*H*-imidazol-1-yl)ethyl-amino]biphenyl-2-ylcarboxamido]-4-(methylsulfonyl)-butyric acid

N-[5-[1-(4-Fluorophenyl)-2-(1*H*-imidazol-1-yl)ethyl-amino]biphenyl-2-ylcarbonyl]-L-methionine



C29 H29 F N4 O3 S; Mol wt: 532.6371

ACTION – Imidazole protein farnesyltransferase inhibitor (IC₅₀ ~ 2 nM) particularly useful in the treatment of cancer.

SOURCE – AstraZeneca.

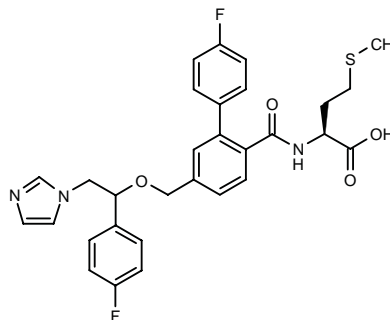
REFERENCES

1. Arnould, J.-C. (Zeneca Ltd.) *Imidazole derivs. and their use as farnesyl protein transferase inhibitors*. WO 9920612.

276174

2(*S*)-[4'-Fluoro-5-[1-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-ethoxymethyl]biphenyl-2-ylcarboxamido]-4-(methylsulfonyl)butyric acid

N-[4'-Fluoro-5-[1-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-ethoxymethyl]biphenyl-2-ylcarbonyl]methionine



C30 H29 F2 N3 O4 S; Mol wt: 565.6381

ACTION – Imidazole protein farnesyltransferase inhibitor (IC₅₀ ~ 1 nM) particularly useful in the treatment of cancer.

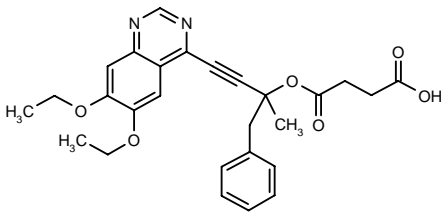
SOURCE – AstraZeneca.

REFERENCES

1. Arnould, J.-C. (Zeneca Ltd.) *Imidazole deris. and their use as farnesyl protein transferase inhibitors*. WO 9920611.

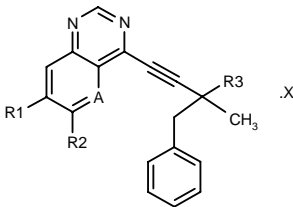
276435

Succinic acid 1-benzyl-3-(6,7-diethoxyquinazolin-4-yl)-1-methyl-2-propynyl monoester

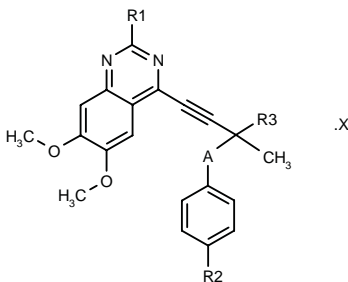


C27 H28 N2 O6; Mol wt: 476.5262

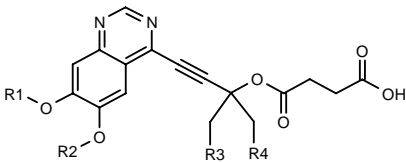
ACTION – Antiproliferative agent with tyrosine kinase-inhibitory activity proven to inhibit epidermal growth factor (EGF) receptor tyrosine kinase from human squamous cell carcinoma A431 cells with an IC₅₀ value of 0.0097 μM and the growth of human nasopharyngeal cancer KB cells expressing the EGF receptor with an IC₅₀ of 0.36 μM. Other representative ethynylpyrimidine derivatives include the following:



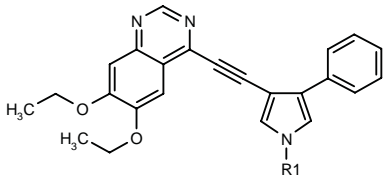
Compound	R1	R2	R3	A	X	Formula
276438	H	H	N(Et)2	CH	HCl	C ₂₃ H ₂₅ N ₃ ·HCl
276447		-OCH2O-	N(Et)2	CH		C ₂₄ H ₂₅ N ₃ O ₂
276450	H	N(Me)2	4-CO2H-1-Pip	N		C ₂₆ H ₂₉ N ₅ O ₂



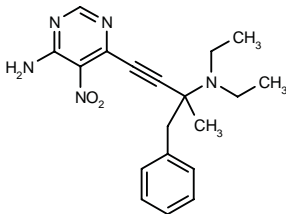
Compound	R1	R2	R3	A	X	Formula
276440	H	F	OH	CH2		C ₂₁ H ₁₉ FN ₂ O ₃
276442	H	H	OH	CH2		C ₂₁ H ₂₀ N ₂ O ₃
276443	H	H	OAc	CH2		C ₂₃ H ₂₂ N ₂ O ₄
276449	H	Me	Me	O		C ₂₂ H ₂₂ N ₂ O ₃
276451	F	H	N(Et)2	CH2	HCl	C ₂₅ H ₂₆ FN ₃ O ₂ ·HCl



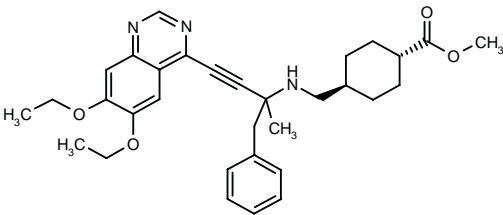
Compound	R1=R2	R3	R4	Formula
276452	i-Pr	Ph	H	C ₂₉ H ₃₂ N ₂ O ₆
276453	Et	4-F-Ph	H	C ₂₇ H ₂₇ FN ₂ O ₆
276454	Et	3,4-(Cl)2-Ph	H	C ₂₇ H ₂₆ Cl ₂ N ₂ O ₆
276456	Et	Ph	Me	C ₂₈ H ₃₀ N ₂ O ₆
276459	Et	CH2Ph	H	C ₂₈ H ₃₀ N ₂ O ₆



Compound	R1	Formula
276460	H	C ₂₄ H ₂₄ N ₃ O ₂
276461	Me	C ₂₅ H ₂₃ N ₃ O ₂



276445: C19 H23 N5 O2



276463: C32 H39 N3 O4

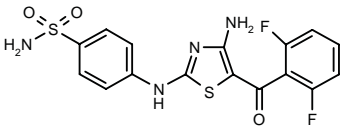
SOURCE – Mitsubishi Chemical.

REFERENCES

1. Kitano, Y. et al. (Mitsubishi Chemical Corp.) *Ethynylpyrimidine derivs.* JP 99080131.

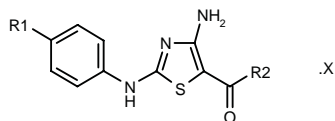
276482

4-[4-Amino-5-(2,6-difluorobenzoyl)thiazol-2-ylamino]-benzenesulfonamide



C16 H12 F2 N4 O3 S2; Mol wt: 410.4238

ACTION – Inhibitor of cyclin-dependent kinases (CDKs) with K_i values of 13 nM, 5.7 nM and 0.0022 μ M, respectively, against CDK4/D, CDK2/A and CDK1/B. Compound also exhibited good cytotoxic activity against a range of tumor cells including HCT-116, U2-OS, Saos-2, COLO-205, M14, RXF-393, MCF-7 and MDA-MB-468 cells (IC_{50} = 0.22-3.9 μ M; IC_{90} = 0.56-13.0 μ M). Other representative compounds from this series of 4-aminothiazole derivatives are:



Compound	R1	R2	X	Formula
276483	SO ₂ NH ₂	3-Me-2-thienyl		C ₁₅ H ₁₄ N ₄ O ₃ S ₃
276484	SO ₂ NH ₂	2,5-(Me)2-3-thienyl		C ₁₆ H ₁₆ N ₄ O ₃ S ₃
276485	4-Me-1-Piz	2,6-(F)2-Ph		C ₂₁ H ₂₁ F ₂ N ₅ OS
276486	1-Piz	2,6-(F)2-Ph	CF ₃ CO ₂ H	C ₂₀ H ₁₉ F ₂ N ₅ OS .C ₂ H ₃ O ₂

SOURCE – Agouron.

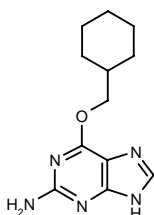
REFERENCES

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NU-2058

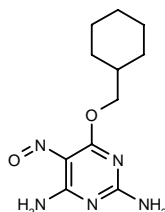
274590

6-(Cyclohexymethoxy)-9H-purin-2-ylamine



C₁₂ H₁₇ N₅ O; Mol wt: 247.3003

ACTION – Cyclin-dependent kinase (CDK) inhibitor with micromolar affinity for both starfish CDK1/cyclin B (IC_{50} = 6 μ M) and human CDK2/cyclin A3 (IC_{50} = 16 μ M). Potentially useful for the treatment of tumors or other proliferative disorders. Another related compound is:



NU-6027 [274670]: C₁₁ H₁₇ N₅ O₂

SOURCES – AstraZeneca; University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

REFERENCES

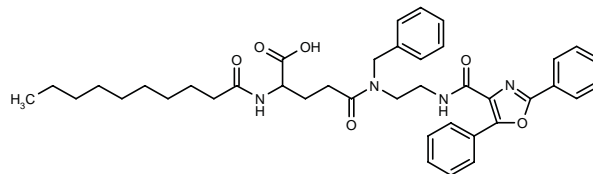
1. Griffin, R.J. et al. (University of Newcastle upon Tyne) *Cyclin dependent kinase inhibiting purine derivs*. WO 9902162.

2. Arris, C.E. et al. *Comparative inhibition of CDK1 and CDK2 by 6-substituted purines and 4-substituted pyrimidines*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2021.

SC- $\alpha\alpha\delta 9$ *

258304

N-Benzyl-N-[2-(2,5-diphenyloxazol-4-ylcarboxamido)-ethyl]-2-(decanamido)glutaramic acid



C₄₀ H₄₈ N₄ O₆; Mol wt: 680.8412

ACTION – Antiproliferative agent, an inhibitor of insulin-like growth factor-1 (IGF-1) receptor autophosphorylation proven to be selectively toxic to virally transformed cells. Compound also inhibited both protein tyrosine phosphatase 1B (PTP1B; IC_{50} < 3 μ M) and Cdc25A dual-specificity phosphatases but did not affect serine/threonine phosphatases or alkaline phosphatase. A lead compound for the development of novel antsignaling agents.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

1. Lazo, J.S. et al. (University of Pittsburgh) *Phosphatase inhibitors and methods of use thereof*. US 5700821, WO 9804257.

2. Vogt, A. et al. *Disruption of insulin-like growth factor-1 signaling and down-regulation of cdc2 by SC- $\alpha\alpha\delta 9$, a novel small molecule antsignaling agent identified in a targeted array library*. J Pharmacol Exp Ther 1998, 287(2): 806.

3. Vogt, A. et al. *Induction of apoptosis in 32D cells by SC- $\alpha\alpha\delta 9$, a novel inhibitor of IGF-1 receptor autophosphorylation*. Proc Amer Assoc Cancer Res 1999, 40: Abst 779.

4. Vogt, A. et al. *Selective toxicity of the Cdc25 inhibitor SC- $\alpha\alpha\delta 9$ is associated with disruption of the IGF-1 receptor signaling pathway*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2160.

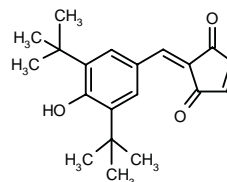
5. Wipf, P. et al. *Combinatorial synthesis and biological evaluation of library of small-molecule Ser/Thr-protein phosphatase inhibitors*. Bioorg Med Chem 1997, 5(1): 165.

*Identified compound **258304** (see **258213**) Drug Data Report 1998, 020(02): 0175.

TX-1123

262556

2-(3,5-Di-*tert*-butyl-4-hydroxyphenylmethylene)-4-cyclopentene-1,3-dione



C₂₀ H₂₄ O₃; Mol wt: 312.4066

ACTION – Antineoplastic agent, an Src protein tyrosine kinase inhibitor ($IC_{50} = 2.2 \mu M$) with antitumor activity in EMT6/KU cells ($EC_{50} = 60 \mu M$) and without associated mitochondrial cytotoxicity.

SOURCE – University of Tokushima, Tokushima (JP).

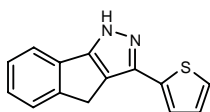
REFERENCES

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2. Hori, H. et al. *TX-1123: A protein tyrosine kinase inhibitor having no mitochondrial cytotoxicity*. Proc Amer Assoc Cancer Res 1999, 40: Abst 774.
3. Ishibashi, K. et al. *Molecular design, synthesis and activity of TX-1123, a protein tyrosine kinase inhibitor, and its derivatives*. 119th Annu Meet Pharm Soc Jpn (March 29-31, Tokushima) 1999, Abst 31(PO)10-072.

ANGIOGENESIS INHIBITORS

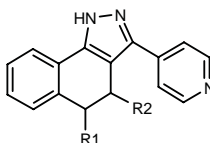
275759

3-(Thien-2-yl)-1,4-dihydroindeno[1,2-*c*]pyrazole



C₁₄ H₁₀ N₂ S; Mol wt: 238.3130

ACTION – Agent for the treatment of angiogenic and hyperproliferative disorders or disorders related to vascular hypermeability that acts by inhibiting the activity of tyrosine kinases, particularly KDR/Fik-1/VEGFR-2 (vascular endothelial growth factor receptor 2) tyrosine kinases ($IC_{50} = 0.15 \mu M$). In addition, compound was shown to inhibit VEGF-induced KDR phosphorylation and VEGF-stimulated mitogenesis in human umbilical vein endothelial cell (HUVEC) cultures with IC_{50} values of 3.0 and 2.0 μM , respectively. Other preferred compounds from this series of indeno[1,2-*c*]-, naphtho[1,2-*c*]- and benzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives include the following:



Compound	R1	R2	Formula
275760	H	H	C ₁₈ H ₁₃ N ₃
275761	bond		C ₁₆ H ₁₁ N ₃

SOURCE – BASF.

REFERENCES

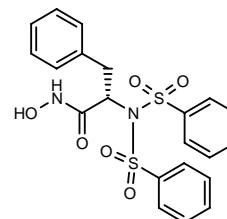
1. Arnold, L.D. et al. (BASF AG) *Indeno[1,2-*c*]-, naphtho[1,2-*c*]- and benzo[6,7]cyclohepta[1,2-*c*]pyrazole derivs*. WO 9917769.

BPHA

276015

2(*S*)-[Bis(phenylsulfonyl)amino]-*N*-hydroxy-3-phenylpropionamide

N,N-Bis(phenylsulfonyl)-*L*-phenylalanine *N*-hydroxyamide



C₂₁ H₂₀ N₂ O₆ S₂; Mol wt: 460.5290

ACTION – Antineoplastic agent, an inhibitor of matrix metalloproteinases (MMPs), especially gelatinase A (MMP-2; $IC_{50} = 12 \text{ nM}$), gelatinase B (MMP-9; $IC_{50} = 16 \text{ nM}$) and MMP-14 ($IC_{50} = 17 \text{ nM}$). Compound (200 mg/kg p.o.) showed significant activity (79% reduction of total vascular area) against human fibrosarcoma HT-1080-induced angiogenesis in mice, significant tumor growth inhibition in mice bearing murine B16-BL6 melanoma (48%) and hemangioendothelioma F2 (45%), and significant inhibition of the formation of liver metastases in a human colon cancer (C-1H) xenograft model (42%), with no toxic effects on body weight or hematopoietic cells at this dose.

SOURCE – Shionogi.

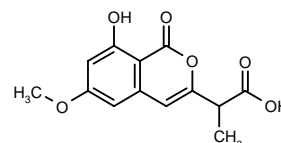
REFERENCES

1. Maekawa, R. et al. *Correlation of antiangiogenic and antitumor efficacy of *N*-biphenyl sulphonyl-phenylalanine hydroxamic acid (BPHA), an orally-active, selective matrix metalloproteinase inhibitor*. Cancer Res 1999, 59(6): 1231.

NM-3*

242688

2-(8-Hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl)propionic acid



C₁₃ H₁₂ O₆; Mol wt: 264.2318

ACTION – Antiangiogenic agent proven to significantly and dose-dependently (0.3-10 mg/kg/day p.o.) inhibit angiogenesis induced by malignant S-180 tumor cells implanted s.c. in mice. *In vitro*, compound showed weak inhibition (50% at 100 μM) of the proliferation of human umbilical vein endothelial cells. Potentially useful for the treatment of angiogenesis-associated diseases such as solid tumors and rheumatoid arthritis.

SOURCE – Mercian.

REFERENCES

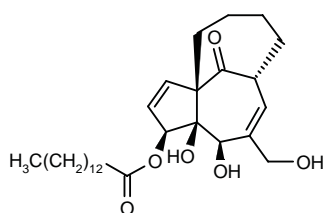
1. Hirano, S. et al. (Mercian Corp.) *Isocoumarin derivs. and use thereof in drugs*. WO 9748693.
2. Hirano, S. et al. (Mercian Corp.) *Isocoumarin derivs*. JP 96176138.
3. Nakashima, T. et al. *Inhibition of angiogenesis by a new isocoumarin, NM-3*. J Antibiot 1999, 52(4): 426.

*Identified compound **242688** (see **240646**) Drug Data Report 1996, 018(11): 1017.

OTHER ONCOLYTIC DRUGS

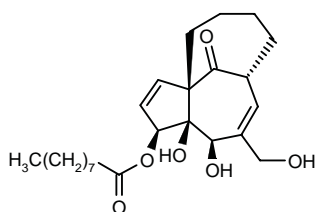
274753

Tetradecanoic acid (1*S**,3*aS**,8*R**,11*R**,11*aS**)-11,11a-dihydroxy-10-(hydroxymethyl)-12-oxo-3*a*,8-methano-1,4,5,6,7,8,11,11a-octahydro-3*aH*-cyclopentacyclodecen-1-yl ester



C29 H46 O6; Mol wt: 490.6764

ACTION – Potent protein kinase C (PKC) activator, an ingenol analogue proven to inhibit the binding of [³H]-PDBU to PKC- α with a K_i of 25 nM. Potentially useful for the treatment of proliferative and inflammatory disorders. Another related compound is:



274754: C24 H36 O6

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Winkler, J.D. et al. *Synthesis and biological evaluation of highly functionalized analogues of ingenol*. J Am Chem Soc 1999, 121(2): 296.

275284

Human rhombotin-like protein

RBTNH

ACTION – A human rhombotin-like protein (RBTNH) produced by recombinant DNA technology. Agonists, antibodies or antagonists to RBTNH, as well as antisense molecules targeting the protein, are also described for the prevention and treatment of diseases associated with the expression of RBTNH including cancer.

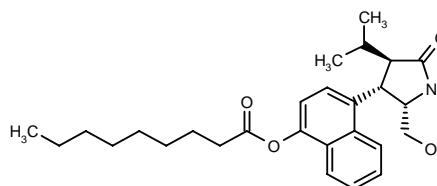
SOURCE – Incyte.

REFERENCES

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275332

Nonanoic acid 4-[2(*S*)-Hydroxymethyl-4(*R*)-isopropyl-5-oxopyrrolidin-3(*S*)-yl]-1-naphthalenyl ester



C27 H37 N O4; Mol wt: 439.5923

ACTION – Antineoplastic agent that acts by activating protein kinase C (PKC; $K_i = 0.3 \pm 0.01 \mu\text{M}$). A specifically claimed compound within a series of substituted 2-pyrrolidinone derivatives.

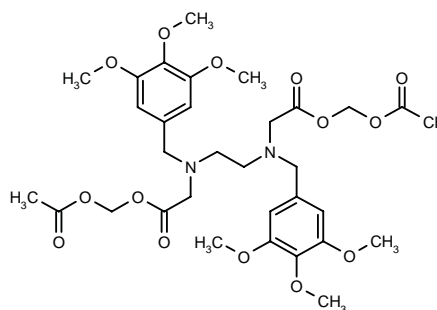
SOURCE – Georgetown University, Washington, D.C. (US).

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1. Kozikowski, A.P. et al. (Georgetown University) *Substd. 2-pyrrolidinone activators of PKC*. WO 9912901.

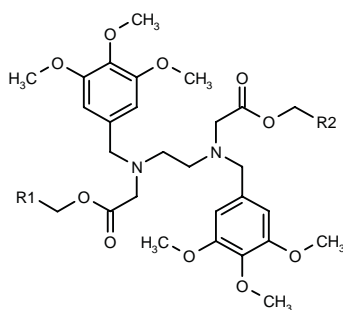
275379

3,6-Bis(3,4,5-trimethoxybenzyl)-3,6-diazaoctanedioic acid bis(acetoxymethyl)diester



C32 H44 N2 O14; Mol wt: 680.6996

ACTION – Antioxidant for the relief of oxidative stress in pathological conditions such as cancer, inflammation, ischemia-reperfusion, neurodegenerative disorders and UV radiation damage. *In vitro*, it was shown to protect V79 cells from H₂O₂-induced toxicity by 50% at 10 μM . Other specifically claimed compounds from this series of diamine alkylene diacetic or triacetic acid derivatives include the following:



Compound	R1=R2	Formula
275380	t-BuCOO	C ₃₈ H ₅₆ N ₂ O ₁₄
275381	CON(Et)2	C ₃₈ H ₅₈ N ₄ O ₁₂

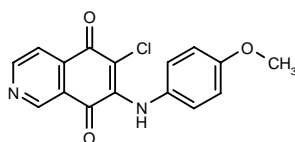
SOURCE – L'Oreal.

REFERENCES

1. Galey, J.-B. and Dumats, J. (L'Oreal) *Novel diamine alkylene diacetic or triacetic acid derivs., preparation method, use in cosmetic and pharmaceutical compsns. and compsns. containing them.* WO 9912891.

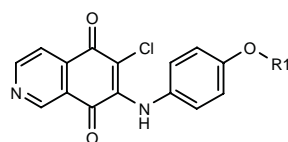
275551

6-Chloro-7-(4-methoxyphenylamino)isoquinoline-5,8-dione



C₁₆H₁₁ClN₂O₃; Mol wt: 314.7269

ACTION – Antineoplastic agent with *in vitro* cytotoxicity against a variety of human solid tumor cell lines such as non-small cell lung A-549, ovarian SK-OV-3 and CNS XF498 cells (IC₅₀ = 0.28-0.5 µg/ml); compound showed exceptional cytotoxic activity against melanoma SK-MEL-2 and colon carcinoma HCT-15 cells (IC₅₀ = 0.02 µg/ml). Its activity was comparable to that of streptonigrin and approximately 50-150-fold superior to that of cisplatin. Other compounds from this series of 6,7-disubstituted-5,8-isoquinolinediones include the following:



Compound	R1	Formula
275550	H	C ₁₈ H ₉ ClN ₂ O ₃
275552	Et	C ₁₇ H ₁₃ ClN ₂ O ₃

SOURCES – Ewha Womans University, Seoul (KR); Korea Research Institute of Chemical Technology, Taejeon (KR).

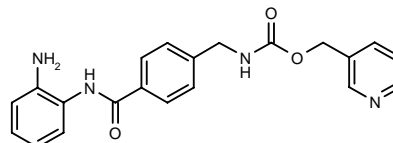
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MS-27-275*

266686

N-[4-[*N*-(2-Aminophenyl)carbamoyl]benzyl]carbamic acid 3-pyridylmethyl ester



C₂₁H₂₀N₄O₃; Mol wt: 376.4140

ACTION – Antineoplastic agent, an inhibitor of human histone deacetylase (HDA; IC₅₀ = 2.0 µM) with a broad spectrum of activity against a variety of human cancer cell lines (IC₅₀ ranging from 0.0415 to 4.71 µM). Compound increased intracellular contents of p21^{WAF1/CIP1} and gelsolin and changed the cell cycle distribution, decreasing S-phase cells and increasing G1-phase cells. Following oral administration (12.3-49 mg/kg), it strongly inhibited the growth of several 5-FU-resistant tumor lines implanted into nude mice.

SOURCES – Mitsui Chemicals; Mitsui Pharmaceuticals.

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2. Saito, A. et al. *A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors.* Proc Natl Acad Sci USA 1999, 96(8): 4592.

*Identified compound **266686** (see **265432**) Drug Data Report 1998, 020(10): 0892.

NHTS

275285

Novel human tumor suppressor protein

ACTION – Human tumor suppressor protein with 89% homology to the murine tumor suppressor gene 101 (tsg 101). This protein is expressed in immortalized or cancerous cells and tissues, particularly lymphoma and cancers of the brain, breast, colon, heart, kidney, ovary, paraganglia, pancreas, prostate, skin, stomach and thyroid, and it is also expressed in lymphocytes and macrophages, as well as in cells and tissues from patients with autoimmune diseases such as asthma, biliary cirrhosis, Crohn's disease, diabetes and rheumatoid arthritis. It is thus expected to be potentially useful for the treatment, prevention and diagnosis of cancer and autoimmune diseases. Agonists and antagonists of NHTS and antisense sequences to polynucleotides encoding NHTS are also described as useful for the treatment of diseases associated with the expression of NHTS.

SOURCE – Incyte.

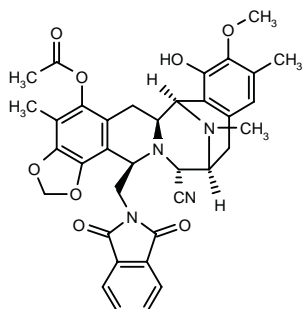
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PHTHALASCIDIN

274209

(6a*S*,7*R*,13*S*,14*S*,16*R*)-5-Acetoxy-14-cyano-8-hydroxy-9-methoxy-4,10,17-trimethyl-16-(*N*-phthalimidomethyl)-6a,7,12,13,14,16-hexahydro-6*H*-7,13-imino-1,3-dioxolo[4',5':7,8]isoquino[3,2-*b*][3]benzazocine



C36 H34 N4 O8; Mol wt: 650.6846

ACTION – Antineoplastic agent structurally related to ecteinascidin 743, but more easily synthesized and more stable than the latter. Compound showed potent antiproliferative activity ($IC_{50} = 0.1-1$ nM) against 8 human cancer cell lines including lung (A-549, NCI-H522), colon (HCT116, COLO205), breast (MCF-7, T-47D) and prostate (PC-3) carcinomas and malignant melanoma (A375). It was highly cytotoxic against A375 and T-47D cell lines and about 1-3 orders of magnitude more potent than several clinically used drugs such as paclitaxel, doxorubicin, camptothecin, mitomycin C, cisplatin, bleomycin and etoposide. Although it induced time-dependent DNA–protein crosslinking and appeared to interact with topoisomerase I, but not II, this protein may not be the compound's primary target.

SOURCES – Harvard University, Cambridge, MA (US); Howard Hughes Medical Institute, Chevy Chase, MD (US).

REFERENCES

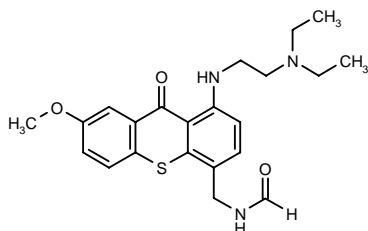
1. Martinez, E.J. et al. *Phthalascidin, a synthetic antitumor agent with potency and mode of action comparable to ecteinascidin 743*. Proc Natl Acad Sci USA 1999, 96(7): 3496.

SR-271425

274453

N-[1-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9*H*-thioxanthen-4-ylmethyl]formamide

1-[2-(Diethylamino)ethylamino]-4-(formamidomethyl)-7-methoxy-9*H*-thioxanthen-9-one



C22 H27 N3 O3 S; Mol wt: 413.5393

M.p 95-9 °C.

ACTION – Antineoplastic agent with a broad spectrum of activity against murine solid tumors and reported to be equally active following p.o. and i.v. administration. In particular, at the optimum i.v. dose compound completely inhibited the growth of murine pancreatic adenocarcinoma 03, advanced-stage colon 38, B16 melanoma, mammary carcinoma 16, colon 26, colon 51, pancreatic adenocarcinoma 02 and mammary carcinoma 17, and it produced cures in all treated mice with Panc 03 tumors. In contrast to its strong *in vivo* activity, compound showed very low *in vitro* cytotoxicity against leukemia P388 ($IC_{50} = 106$ μM) and only weak inhibition of topoisomerase II ($EC_{50} > 480$ μM).

SOURCE – Sanofi-Synthelabo.

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2. Corbett, T.H. et al. *Preclinical antitumor activity of thioxanthenone SR 271425*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2624.
3. Perni, R.B. et al. *Synthesis and antitumor activity of 4-aminomethylthioxanthenone and 5-aminomethylbenzothiopyranindazole derivatives*. J Med Chem 1998, 41(19): 3645.
4. Wentland, M.P. et al. *Anti-solid tumor efficacy and preparation of *N*-[1-[2-(diethylamino)ethylamino]-9-oxo-9*H*-thioxanthen-4-yl]methyl]methanesulfonamide (WIN 33377) and related derivatives*. Bioorg Med Chem Lett 1994, 4(4): 609.

CANCER GENE THERAPY

275815

20-mer phosphorothioate oligodeoxynucleotide in which the 6 nucleotides on either end of the oligomer are 2'-methoxyethoxylated and the middle 8 are not, whose sequence is: 5'-GCCAGTGGCAACATCCTTAA-3'

ACTION – Antisense oligodeoxynucleotide targeted to sequences on the 3' end of thymidylate synthase (TS) mRNA, for use in downregulating TS mRNA translation or protein expression, resulting in cell proliferation inhibition; additionally, it can be used to enhance cytotoxicity of TS inhibitors. Results of *in vitro* tests showed that compound inhibits the growth of HeLa cells in a concentration-dependent manner when formulated in liposomes; additionally, it enhanced the sensitivity of these cells to the toxic effects of 5-FU, 5-FUdR, raltitrexed (Tomudex) and methotrexate, but not cisplatin or chlorambucil.

SOURCES – AstraZeneca; Isis Pharmaceuticals.

REFERENCES

1. Koropatnick, D.J. et al. (Zeneca Ltd./Isis Pharmaceuticals, Inc.) *Antisense oligonucleotides against thymidylate synthase*. WO 9915648.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

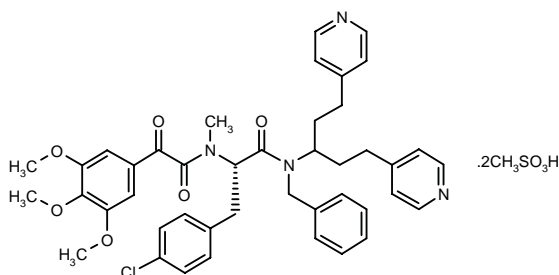
TIMCODAR DIMESILATE*

Prop INN

235419**237979** (as free base)

*N*¹-Benzyl-4-chloro-*N*²-methyl-*N*²-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]-*N*¹-[3-(4-pyridyl)-1-[2-(4-pyridyl)-ethyl]propyl]-L-phenylalaninamide dimethanesulfonate

VX-853



C43 H45 Cl N4 O6 . 2 C H4 O3 S; Mol wt: 941.5147

ACTION – Orally active multidrug resistance (MDR) inhibitor that blocks both P-glycoprotein (MDR1) and multidrug resistance-associated protein (MRP). Compound restores sensitivity to doxorubicin, vincristine, etoposide and paclitaxel in a variety of MDR1- and MRP-expressing MDR cells. It is undergoing phase I/II evaluation. Compound also acts as a neurophilin ligand that stimulates nerve growth in models of central and peripheral nerve injury, and is in phase II testing for the treatment of diabetic neuropathy.

SOURCE – Vertex.

REFERENCES

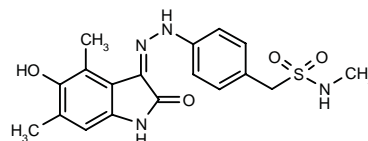
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4. *First clinical trial of oral neurophilin compound in patients with diabetic neuropathy.* DailyDrugNews.com (Daily Essentials) 1998, Nov 11.
5. *Preliminary clinical data presented at AACR meeting on Vertex's lead cancer multidrug resistance compound, VX-710 - Vertex begins clinical trial for second MDR compound.* Vertex Pharmaceuticals Inc. Press Release 1996, April 24.
6. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 279.
7. *Vertex announces start of clinical trial with VX-745 as new drug candidate targeting inflammatory and neurological diseases.* Vertex Pharmaceuticals Inc. Press Release 1999, March 9.
8. *Vertex Pharmaceuticals begins phase II clinical trial of neurophilin compound, targeting treatment of peripheral neuropathies - First-ever clinical trial of orally active neurophilin ligand, in patients with diabetic neuropathy.* Vertex Pharmaceuticals Inc. Press Release 1998, Nov 10.
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*Identified compound **237979** Drug Data Report 1996, 018(09): 0840.

CHEMOPROTECTIVE AGENTS

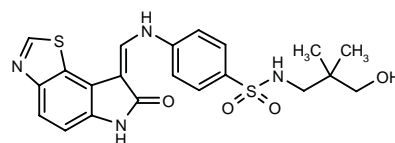
275644

4-[2-(5-Hydroxy-4,6-dimethyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazino]-*N*-methylbenzylsulfonamide



C18 H20 N4 O4 S; Mol wt: 388.4460

ACTION – Inhibitor of protein tyrosine kinases and protein serine/threonine kinases, particularly active against the cyclin-dependent kinases CDK1 and CDK2, and therefore of particular utility in the treatment of alopecia associated with cancer chemotherapy. Also potentially useful for the treatment of organ transplant rejection, chemotherapy-induced thrombocytopenia or leukopenia and for inhibiting tumor growth, as well as for treating mucositis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy, psoriasis, diabetes mellitus, inflammation, neurodegenerative diseases, macular degeneration, actinic keratosis and hyperproliferative disorders. Another representative compound within this series of specifically claimed substituted oxindole derivatives is:

**275645:** C21 H22 N4 O4 S2**SOURCE** – Glaxo Wellcome.

REFERENCES

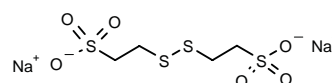
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BNP-7787

238062

2,2'-Dithiobis(ethanesulfonic acid) disodium salt

Dimesna
Mesna disulfide



C4 H8 O6 S4 . 2 Na; Mol wt: 326.3452

ACTION – Chemoprotective agent able to prevent or decrease the clinical toxicities (including neurotoxicity, nephrotoxicity, myelosuppression, nausea and emesis) of anticancer drugs such as taxanes and platinum-based agents; compound itself is devoid of antitumor effect. Preclinical studies in rats demonstrated that oral or i.v. pretreatment with BNP-7787 protected against platinum- and paclitaxel-associated neurotoxicity without affecting antitumor activity; it appears to protect against platinum- and taxane-associated tubulin toxicity; increasing levels of compound resulted in increasing levels of tubulin protection. It exhibited a good safety profile in phase I clinical studies at dose levels up to 23 g/m², and at high doses it did not interfere with the pharmacokinetics of cisplatin.

SOURCES – BioNumerik; Grelan.

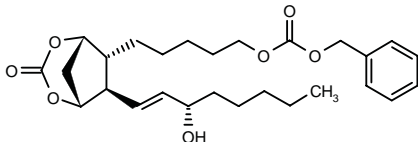
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OCULAR MEDICATIONS

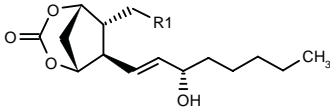
275261

Benzyl 5-[(1*R*,5*S*,6*R*,7*R*)-7-[3(*S*)-hydroxy-1(*E*)-octenyl]-3-oxo-2,4-dioxabicyclo[3.2.1]oct-6-yl]pentyl carbonate



C27 H38 O7; Mol wt: 474.5902

ACTION – Antiglaucoma agent expected to reduce ocular pressure by virtue of its thromboxane receptor-antagonist activity. Other specifically claimed compounds include the following:



Compound	R1	Formula
275262	(Z)-CH=CHCH2CH2OCO2-allyl	C ₂₃ H ₃₄ O ₇
275263	(CH2)4OCO2H	C ₂₀ H ₃₂ O ₇
275264	(Z)-CH=CHCH2CH2OCO2H	C ₂₀ H ₃₀ O ₇
275265	(Z)-CH=CHCH2CH2OCH2OH	C ₂₀ H ₃₂ O ₆
275266	(CH2)4OCH2OH	C ₂₀ H ₃₄ O ₆

SOURCE – Allergan.

REFERENCES

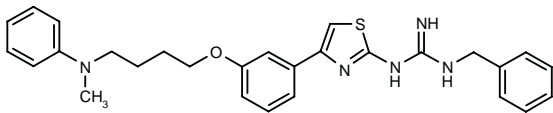
1. Burk, R.M. (Allergan, Inc.) *Thromboxane ligands*. WO 9912921.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

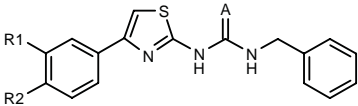
275196

N-Benzyl-*N*'-[4-[3-[4-(*N*-methyl-*N*-phenylamino)butoxy]-phenyl]thiazol-2-yl]guanidine



C28 H31 N5 O S; Mol wt: 485.6529

ACTION – Cysteine protease inhibitor particularly active against cathepsin K activity, claimed for use in the treatment of osteoporosis, periodontitis, gingivitis, osteoarthritis and rheumatoid arthritis. Other specifically claimed thiazoleguanidine derivatives include the following:



Compound	R1	R2	A	Formula
275197	3,4-(Cl)2-Ph-N(Me)(CH2)3O	H	NH	C ₂₇ H ₂₇ Cl ₂ N ₅ OS
275198	4-Br-Ph-N(Me)(CH2)4O	H	NH	C ₂₈ H ₃₀ BrN ₅ OS
275199	1-Piz-(CH2)4O	H	NH	C ₂₅ H ₃₂ N ₆ OS
275200	H	3,4-(Cl)2-Ph-N(Me)(CH2)3O	O	C ₂₇ H ₂₆ Cl ₂ N ₄ O ₂ S
275201	H	3,4-(Cl)2-Ph-N(COOCH2Ph)(CH2)3O	NH	C ₃₄ H ₃₁ Cl ₂ N ₅ O ₃ S

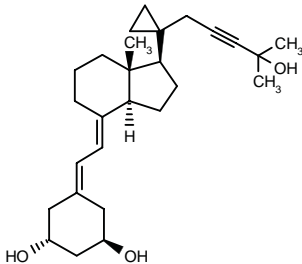
SOURCE – SmithKline Beecham.

REFERENCES

1. Christensen, S.B. IV et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9911637.

275355

1α,25-Dihydroxy-20,21-methylene-19-nor-23,23,24,24-tetradehydrovitamin D₃



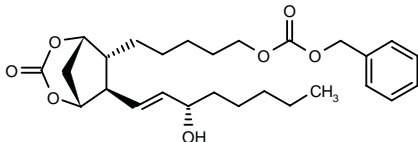
C27 H40 O3; Mol wt: 412.6100

ACTION – Vitamin D₃ analogue with potential in the treatment of osteoporosis, cancer and secondary hyperparathyroidism. In ovariectomized rats, compound was more effective at 0.010 μg/kg/day p.o. than 1,25-dihydroxyvitamin D₃ at 0.200 μg/kg/day p.o. in increasing bone mineral density. In addition, it was more potent than 1,25-dihydroxyvitamin D₃ in inhibiting the growth of human breast cancer MCF-7 and ZR-75 cells (IC₅₀ = 0.03 and 0.01 nM vs. 149 and 13 nM, respectively) and was shown to be more effective than 1,25-dihydroxyvitamin D₃ in suppressing parathyroid hormone in a rat renal failure model when given at doses of 0.1 μg/kg/day p.o. Another specifically claimed compound from this series of 1,3-dihydroxy-20,20-dialkylvitamin D₃ analogues is:

OCULAR MEDICATIONS

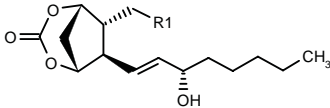
275261

Benzyl 5-[(1*R*,5*S*,6*R*,7*R*)-7-[3(*S*)-hydroxy-1(*E*)-octenyl]-3-oxo-2,4-dioxabicyclo[3.2.1]oct-6-yl]pentyl carbonate



C27 H38 O7; Mol wt: 474.5902

ACTION – Antiglaucoma agent expected to reduce ocular pressure by virtue of its thromboxane receptor-antagonist activity. Other specifically claimed compounds include the following:



Compound	R1	Formula
275262	(Z)-CH=CHCH2CH2OCO2-allyl	C ₂₃ H ₃₄ O ₇
275263	(CH2)4OCO2H	C ₂₀ H ₃₂ O ₇
275264	(Z)-CH=CHCH2CH2OCO2H	C ₂₀ H ₃₀ O ₇
275265	(Z)-CH=CHCH2CH2OCH2OH	C ₂₀ H ₃₂ O ₆
275266	(CH2)4OCH2OH	C ₂₀ H ₃₄ O ₆

SOURCE – Allergan.

REFERENCES

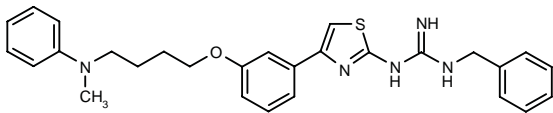
1. Burk, R.M. (Allergan, Inc.) *Thromboxane ligands*. WO 9912921.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

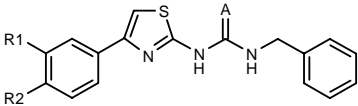
275196

N-Benzyl-*N*'-[4-[3-[4-(*N*-methyl-*N*-phenylamino)butoxy]-phenyl]thiazol-2-yl]guanidine



C28 H31 N5 O S; Mol wt: 485.6529

ACTION – Cysteine protease inhibitor particularly active against cathepsin K activity, claimed for use in the treatment of osteoporosis, periodontitis, gingivitis, osteoarthritis and rheumatoid arthritis. Other specifically claimed thiazoleguanidine derivatives include the following:



Compound	R1	R2	A	Formula
275197	3,4-(Cl)2-Ph-N(Me)(CH2)3O	H	NH	C ₂₇ H ₂₇ Cl ₂ N ₅ OS
275198	4-Br-Ph-N(Me)(CH2)4O	H	NH	C ₂₈ H ₃₀ BrN ₅ OS
275199	1-Piz-(CH2)4O	H	NH	C ₂₅ H ₃₂ N ₆ OS
275200	H	3,4-(Cl)2-Ph-N(Me)(CH2)3O	O	C ₂₇ H ₂₆ Cl ₂ N ₄ O ₂ S
275201	H	3,4-(Cl)2-Ph-N(COOCH2Ph)(CH2)3O	NH	C ₃₄ H ₃₁ Cl ₂ N ₅ O ₃ S

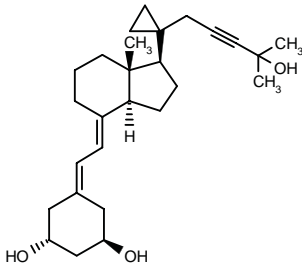
SOURCE – SmithKline Beecham.

REFERENCES

1. Christensen, S.B. IV et al. (SmithKline Beecham Corp.) *Protease inhibitors*. WO 9911637.

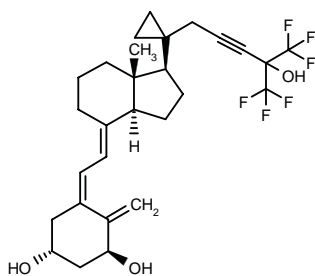
275355

1α,25-Dihydroxy-20,21-methylene-19-nor-23,23,24,24-tetradehydrovitamin D₃



C27 H40 O3; Mol wt: 412.6100

ACTION – Vitamin D₃ analogue with potential in the treatment of osteoporosis, cancer and secondary hyperparathyroidism. In ovariectomized rats, compound was more effective at 0.010 µg/kg/day p.o. than 1,25-dihydroxyvitamin D₃ at 0.200 µg/kg/day p.o. in increasing bone mineral density. In addition, it was more potent than 1,25-dihydroxyvitamin D₃ in inhibiting the growth of human breast cancer MCF-7 and ZR-75 cells (IC₅₀ = 0.03 and 0.01 nM vs. 149 and 13 nM, respectively) and was shown to be more effective than 1,25-dihydroxyvitamin D₃ in suppressing parathyroid hormone in a rat renal failure model when given at doses of 0.1 µg/kg/day p.o. Another specifically claimed compound from this series of 1,3-dihydroxy-20,20-dialkylvitamin D₃ analogues is:



275356: C₂₈ H₃₄ F₆ O₃

SOURCE – Roche.

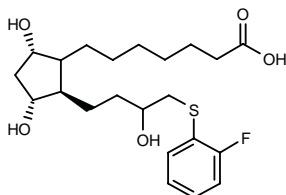
REFERENCES

1. Manchand, P.S. and Uskokovic, M.R. (F. Hoffmann-La Roche AG) *1,3-Dihydroxy-20,20-dialkyl-vitamin D₃ analogs*. WO 9912894.

275382

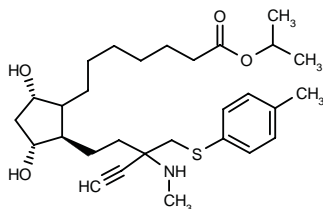
7-[(2*R*,3*R*,5*S*)-2-[4-(2-Fluorophenylsulfanyl)-3-hydroxybutyl]-3,5-dihydroxycyclopentyl]heptanoic acid

16-(2-Fluorophenylsulfanyl)-13,14-dihydro-17,18,19,20-tetranorprostaglandin F_{1α}



C₂₂ H₃₃ F O₅ S; Mol wt: 428.5617

ACTION – Prostaglandin F analogue useful as an FP receptor agonist, with potential in the treatment of bone disorders and glaucoma; compound is reported to possess advantages over existing bone disorder therapies by virtue of its ability to increase trabecular number through formation of new trabeculae, increase bone mass and bone volume while maintaining a more normal bone turnover rate, as well as its ability to increase bone formation at the endosteal surface without increasing cortical porosity. Another compound from this series of aromatic C16-C20-substituted tetrahydroprostaglandin derivatives is:



275383: C₂₉ H₄₅ N O₄ S

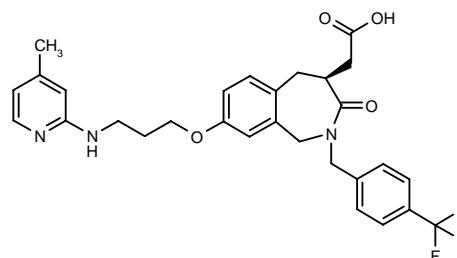
SOURCE – Procter & Gamble.

REFERENCES

1. Wos, J.A. et al. (The Procter & Gamble Co.) *Aromatic C16-C20-substd. tetrahydro prostaglandins useful as FP agonists*. WO 9912895.

275594

2-[8-[3-(4-Methylpyridin-2-ylamino)propoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4(*S*)-yl]acetic acid



C₂₉ H₃₀ F₃ N₃ O₄; Mol wt: 541.5670

ACTION – Agent for the treatment of osteoporosis, inflammation, cancer and cardiovascular disorders such as atherosclerosis and restenosis, a vitronectin ($\alpha_v\beta_3$ and $\alpha_v\beta_5$) receptor antagonist ($K_i = 0.003 \mu\text{M}$ against [³H]-SK&F-10726 binding to human placenta or platelet $\alpha_v\beta_3$ receptors).

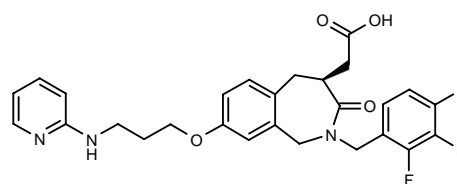
SOURCE – SmithKline Beecham.

REFERENCES

1. Miller, W.H. (SmithKline Beecham Corp.) *Vitronectin receptor antagonist*. WO 9915170.

275664

2-[3-Oxo-8-[3-(2-pyridinylamino)propoxy]-2-(2,3,4-trifluorobenzyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4(*S*)-yl]acetic acid



C₂₇ H₂₆ F₃ N₃ O₄; Mol wt: 513.5134

ACTION – Agent for the treatment of osteoporosis, inflammation, cancer and cardiovascular disorders such as atherosclerosis and restenosis, a vitronectin ($\alpha_v\beta_3$ and $\alpha_v\beta_5$) receptor antagonist proven to inhibit [³H]-SK&F-107260 binding to human $\alpha_v\beta_3$ receptors at a concentration of about 0.003 μM ; it has much lower affinity for fibrinogen (gpIIb/IIIa) receptors.

SOURCE – SmithKline Beecham.

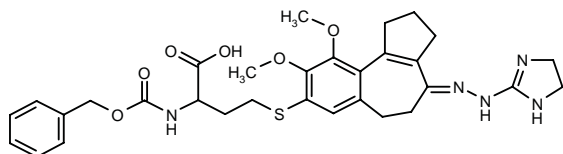
REFERENCES

1. Miller, W.H. (SmithKline Beecham Corp.) *Vitronectin receptor antagonist*. WO 9915178.

275729

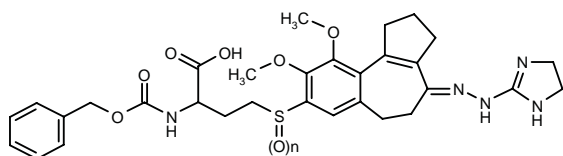
N-Benzyloxycarbonyl-*S*-[4-[2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono]-9,10-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*e*]azulen-8-yl]-DL-homocysteine

2-Benzyloxycarbonylamino-4-[4-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-9,10-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*e*]azulen-8-ylsulfanyl]butyric acid



C₃₁ H₃₇ N₅ O₆ S; Mol wt: 607.7283

ACTION – Integrin $\alpha_v\beta_3$ (vitronectin) receptor antagonist (IC_{50} = 0.040 μ M), potentially useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, inflammation, cancer, atherosclerosis, restenosis and angiogenesis. Other specifically claimed compounds within this series of hydrazono-benzazulene derivatives include the following:



Compound	n	Formula
275730	1	C ₃₁ H ₃₇ N ₅ O ₇ S
275731	2	C ₃₁ H ₃₇ N ₅ O ₈ S

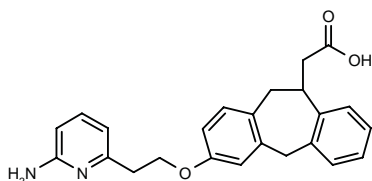
SOURCES – Genentech; Hoechst Marion Roussel.

REFERENCES

1. Camiato, D. et al. (Hoechst Marion Roussel, SA;Genentech, Inc.) *Hydrazono-benzazulene derivs., pharmaceutical compsns. and intermediates*. WO 9915507.

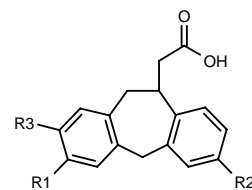
275743

(±)-2-[3-[2-(6-Aminopyridin-2-yl)ethoxy]-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-10-yl]acetic acid

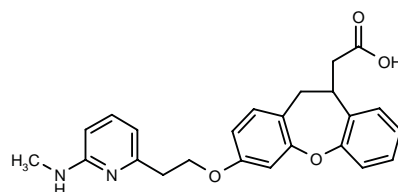


C₂₄ H₂₄ N₂ O₃; Mol wt: 388.4646

ACTION – Agent for the treatment of osteoporosis, cancer, angiogenesis, atherosclerosis, restenosis and inflammation, a selective vitronectin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptor antagonist. Other specifically claimed compounds within this series of tricyclic derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
275744	2-Pyr-NH(CH ₂) ₄	H	H	racemic	C ₂₈ H ₂₈ N ₂ O ₂
275745	2-(EtNH)-4-thiazolyl-CH ₂ CH ₂ O	H	H	racemic	C ₂₄ H ₂₆ N ₂ O ₃ S
275746	1-isoquinolinyl-NH(CH ₂) ₃ O	H	H	racemic	C ₂₉ H ₂₈ N ₂ O ₃
275747	2-Pyr-NH(CH ₂) ₃ O	F	CH ₂ -N(Me) ₂	racemic	C ₂₈ H ₃₂ N ₂ O ₃
275748	4-N(Me)2-2-Pyr-NH(CH ₂) ₃ O	H	H	S	C ₂₇ H ₃₁ N ₃ O ₃



275749: C₂₄ H₂₄ N₂ O₄

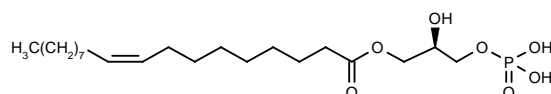
SOURCE – SmithKline Beecham.

REFERENCES

1. Bondinell, W.E. et al. (SmithKline Beecham Corp.) *Vitronectin receptor antagonists*. WO 9915508.

275773

9(*Z*)-Octadecenoic acid 2(*R*)-hydroxy-3-(phosphonoxy)-propyl ester



C₂₁ H₄₁ O₇ P; Mol wt: 436.5219

ACTION – Agent for the treatment of bone metabolic disorders, a lysophosphatidyl acid derivative that acts by stimulating bone formation, as demonstrated *in vitro* by an increase in DNA synthesis rate in fetal rat osteoblasts (161 ± 13% and 284 ± 22% relative to control at 0.3 and 10.0 μ g/ml, respectively), and *in vivo*, where it increased bone mass and X-ray density by 37 and 58%, respectively, at a dose of 0.6 mg/day in mice.

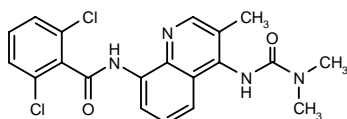
SOURCE – Roche Diagnostics.

REFERENCES

1. Esswein, A. and Kling, L. (Roche Diagnostics GmbH) *Osteoblast-specific mitogens and drugs containing such cpds*. WO 9917781.

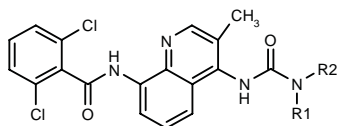
276658

N-[8-(2,6-Dichlorobenzamido)-3-methylquinolin-8-yl]-*N*',*N*'-dimethylurea



C20 H18 Cl2 N4 O2; Mol wt: 417.2942

ACTION – Vacuolar, especially osteoclast, H⁺-ATPase inhibitor proven to potently inhibit vacuolar-type H⁺-ATPase proton transport in mouse peritoneal macrophages (96% at 1 μM), as well as parathyroid hormone (PTH)-induced bone resorption in rat calvariae (100% at 1 μM). Potentially useful for the treatment or prevention of bone diseases caused by abnormal bone metabolism such as osteoporosis, hypercalcemia, hyperparathyroidism, Paget's disease, osteolysis, hypercalcemia of malignancy with or without bone metastasis, rheumatoid arthritis, periodontitis, osteoarthritis, osteopenia, cancer cachexia and malignant tumors. Other exemplified quinoline derivatives include the following:



Compound	R1	R2	Formula
276659	-CH2CH2OCH2CH2-		C ₂₂ H ₂₀ Cl ₂ N ₄ O ₃
276661	H	2-Pyr-CH2	C ₂₄ H ₁₉ Cl ₂ N ₅ O ₂
276664	H	2-thiazolyl	C ₂₁ H ₁₅ Cl ₂ N ₅ O ₂ S
276666	H	CH2CF3	C ₂₀ H ₁₅ Cl ₂ F ₃ N ₄ O ₂

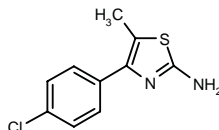
SOURCE – Fujisawa.

REFERENCES

- Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Quinoline derivs. as H⁺-ATPase inhibitors and as bone resorption inhibitors*. WO 9921835.

SCRC-2941-18**275246**

4-(4-Chlorophenyl)-5-methylthiazol-2-amine



C10 H9 Cl N2 S; Mol wt: 224.7141

ACTION – Potent, small-molecule inhibitor of IL-6 secretion *in vitro* (IC₅₀ = 1 μg/ml for inhibition of parathyroid hormone [PTH]-induced IL-6 secretion in osteoblast MC3T3-E1 cells). In ovariectomized mice, compound (2 mg/kg/day i.p. for 4 weeks) significantly suppressed the bone weight loss induced by ovariectomy. Potentially useful for the prevention and treatment of osteoporosis, as well as for the treatment of other diseases related to IL-6 hypersecretion such as multiple myeloma, chronic autoimmune diseases and AIDS.

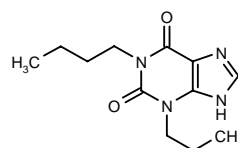
SOURCE – Sagami.

REFERENCES

- Kobori, T. et al. (Sagami Chemical Research Center) *IL-6 production inhibitors, bone resorption inhibitors, and anti-osteoporosis agents and thiazole cpds*. JP 98087490.
- Yamaguchi, K. et al. *4-Phenylthiazole derivatives inhibit IL-6 secretion in osteoblastic cells and suppress bone weight loss in ovariectomized mice*. Bioorg Med Chem Lett 1999, 9(7): 957.

XT-44**275497**

1-Butyl-3-propyl-3,9-dihydro-1*H*-purine-2,6-dione



C12 H18 N4 O2; Mol wt: 250.3002

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (K_i = 14.3 μM) with high selectivity over PDE1 and PDE3 (IC₅₀ = 149 and > 300 μM) and high affinity and selectivity for adenosine A₁ over A₂ receptors (K_i = 0.02 and 4.1 μM, respectively). Compound showed high bronchoselectivity *in vitro* (EC₅₀ = 0.03 and 29.1 μM for tracheal relaxation and heart stimulation, respectively) and *in vivo* (ED₅₀ = 2.87 mg/kg i.d. for attenuation of acetylcholine-induced bronchospasm in guinea pigs and ED₁₅ > 100 mg/kg i.d. for positive chronotropic action in guinea pigs). Compound (0.1-10 μM) significantly stimulated mineralized nodule formation in rat bone marrow cultures, and inhibited osteoclast-like cell formation in mouse bone marrow cultures. In three osteopenia models (Walker 256/S carcinosarcoma-bearing rats, sciatic neurectomy in rats and ovariectomy in female rats), oral administration of compound at doses ranging from 0.3 to 1.0 mg/kg every 2 days significantly inhibited the decrease in bone mineral density. Potentially useful for the treatment of osteopenia, including osteoporosis.

SOURCE – Hokuriku.

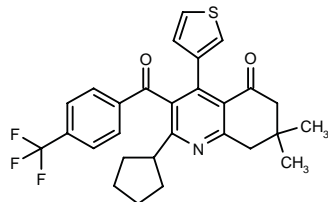
REFERENCES

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- Hiramatsu, K. et al. *Effect of phosphodiesterase IV inhibitors on osteoporosis-like changes in Walker 256/S-bearing rats*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-249.
- Miyamoto, K. et al. *Cyclic nucleotide phosphodiesterase isoenzymes in guinea-pig tracheal muscle and bronchorelaxation by alkylxanthines*. Biochem Pharmacol 1994, 48(6): 1219.
- Myamoto, K. et al. *Effects of alkyl substituents of xanthine on phosphodiesterase isoenzymes*. Biol Pharm Bull 1995, 18(3): 431.
- Sakai, R. et al. *Effects of alkyl substitutions of xanthine skeleton on bronchodilation*. J Med Chem 1992, 35(22): 4039.
- Sanae, F. et al. *Structure-activity relationships of alkylxanthines: Alkyl chain elongation at the N1- or N7-position decreases cardiotonic activity in the isolated guinea pig heart*. Jpn J Pharmacol 1995, 69(2): 75.
- Waki, Y. et al. *Effects of XT-44, a phosphodiesterase 4 inhibitor, in osteoblastogenesis and osteoclastogenesis in culture and its therapeutic effects in rat osteopenia model*. Jpn J Pharmacol 1999, 79(4): 477.
- Yamamoto, K. et al. *Structure-activity relationships of alkylxanthine inhibitors of phosphodiesterase IV isoenzyme*. Biol Pharm Bull 1998, 21(4): 356.

TREATMENT OF LIPOPROTEIN DISORDERS

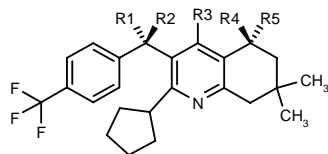
275605

2-Cyclopentyl-7,7-dimethyl-4-(3-thienyl)-3-[4-(trifluoromethyl)benzoyl]-5,6,7,8-tetrahydroquinolin-5-one

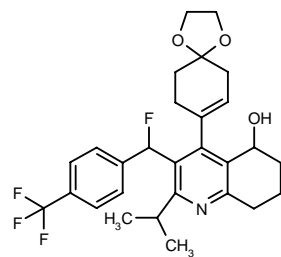


C28 H26 F3 N O2 S; Mol wt: 497.5784

ACTION – Agent for the treatment of arteriosclerosis and dyslipidemia that acts by inhibiting cholesteryl ester transfer protein (CETP; IC₅₀ = 0.01 μM). Within this series of 4-heteroaryl-tetrahydroisoquinolines, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
275606		-O-	4-Pyr		-O-	C ₂₉ H ₂₇ F ₃ N ₂ O ₂
275609		-O-	cyclohexyl		-O-	C ₃₀ H ₃₄ F ₃ NO ₂
275610		-O-	3-thienyl	OH	H	C ₂₈ H ₂₆ F ₃ NO ₂ S
275614	F	H	3-thienyl	OH	H	C ₂₈ H ₂₅ F ₄ NOS
275615	H	H	3-thienyl	OH	H	C ₂₈ H ₃₀ F ₃ NOS



275611: C28 H31 F4 N O3

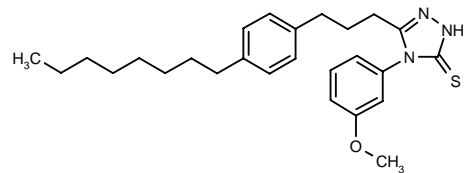
SOURCE – Bayer.

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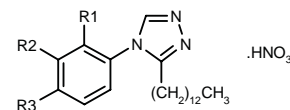
275638

4-(3-Methoxyphenyl)-5-[3-(4-octylphenyl)propyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione

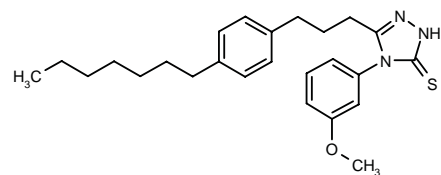


C26 H35 N3 O S; Mol wt: 437.6485

ACTION – Agent for the treatment of dyslipidemia, hyperlipoproteinemia, atherosclerosis and coronary artery disease, an inhibitor of cholesteryl ester transfer protein (CETP; IC₅₀ = 4 μM). Other specifically claimed compounds within this series of substituted 1,2,4-triazoles include the following:



Compound	R1	R2	R3	Formula
275639	H	Me	H	C ₂₂ H ₃₅ N ₃ .HNO ₃
275640	H	OMe	H	C ₂₂ H ₃₅ N ₃ O.HNO ₃
275641	H	H	OMe	C ₂₂ H ₃₅ N ₃ O.HNO ₃
275642	OMe	H	H	C ₂₂ H ₃₅ N ₃ O.HNO ₃
275643	H	-OCH2O-		C ₂₂ H ₃₃ N ₃ O ₂ .HNO ₃
277463	H	-CH=CHCH=CH-		C ₂₅ H ₃₅ N ₃ .HNO ₃



277464: C25 H33 N3 O S

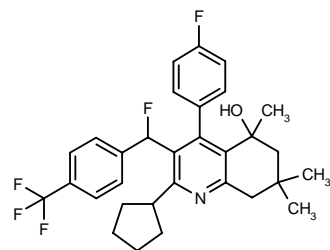
SOURCE – Searle.

REFERENCES

1. Sikorski, J.A. (G.D. Searle & Co.) *Substd. 1,2,4-triazoles useful for inhibiting cholesteryl ester transfer protein activity*. WO 9914204.

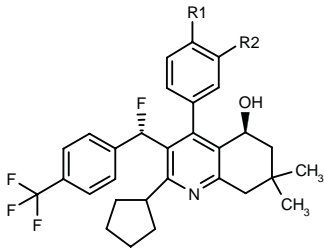
275653

2-Cyclopentyl-4-(4-fluorophenyl)-3-[fluoro[4-(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydroquinolin-5-one



C31 H32 F5 N O; Mol wt: 529.5898

ACTION – Agent for the treatment of arteriosclerosis and dyslipidemia, an inhibitor of cholesteryl ester transfer protein (CETP; IC₅₀ = 0.006 μM). Other representative compounds within this series of 4-phenyltetrahydroquinoline derivatives include the following:



Compound	R1	R2	Formula
275654	Me	H	C ₃₁ H ₃₃ F ₄ NO
275655	H	F	C ₃₀ H ₃₀ F ₅ NO

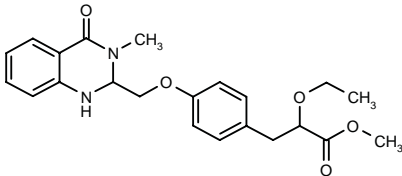
SOURCE – Bayer.

REFERENCES

1. Schmidt, G. et al. (Bayer AG) 4-Phenyltetrahydroquinoline utilized as an inhibitor of the cholesterol ester transfer protein. WO 9915504.

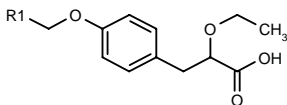
275809

2-Ethoxy-3-[4-(3-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylmethoxy)phenyl]propionic acid methyl ester



C22 H26 N2 O5; Mol wt: 398.4564

ACTION – Agent for the treatment of hyperlipidemia, hypercholesterolemia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance and insulin resistance proven to lower blood glucose and triglyceride levels in *db/db* mice when administered at 3 mg/kg/day p.o. x 6 days (31 and 62% reduction, respectively). It is reported to have the ability to lower total cholesterol and LDL cholesterol levels and increase HDL cholesterol levels, as well as to have agonist activity at peroxisome proliferator-activated receptors α and/or γ (PPARα, PPARγ); compound may also inhibit HMG-CoA reductase activity. Other compounds from this series of β-aryl-α-oxysubstituted alkylcarboxylic acid derivatives include the following:



Compound	R1	Formula
275810	4-oxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl-CH2	C ₂₁ H ₂₃ NO ₆
275811	4-oxo-3,4-dihydro-2H-1,3-benzoxazin-2-yl	C ₂₀ H ₂₁ NO ₆
275812	4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl	C ₂₀ H ₂₂ N ₂ O ₅

SOURCE – Dr. Reddy’s Research Foundation, Hyderabad (IN).

REFERENCES

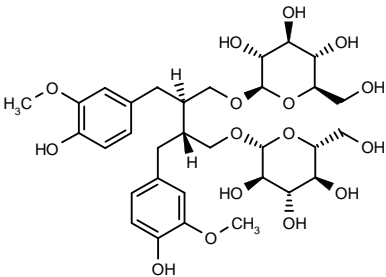
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SECOISOLARICIRESinOL DIGLUCOSIDE

273491

(2*R*,3*R*)-2,3-Bis(4-hydroxy-3-methoxybenzyl)-1,4-butanediylbis(β-D-glucopyranoside)

SDG



C32 H46 O16; Mol wt: 686.6994

ACTION – Hypolipidemic agent, a plant lignan isolated from flaxseed with antioxidant activity. In rabbits fed a high-cholesterol diet, compound administered orally at a dose of 15 mg/kg for 8 weeks reduced total serum cholesterol (33%) and LDL cholesterol levels (35%) and significantly increased (> 140%) HDL cholesterol levels. Moreover, compound reduced the increase in aortic malondialdehyde and atherosclerotic plaques induced by ingestion of a high-cholesterol diet. It was able to attenuate hypercholesterolemic atherosclerosis by reducing oxidative stress and lowering serum cholesterol levels. Potentially useful in preventing hypercholesterolemic atherosclerosis and lowering the risk of coronary artery disease.

SOURCE – University of Saskatchewan, Saskatoon, SK (CA).

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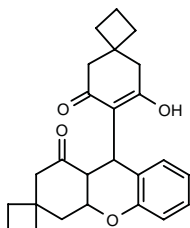
2. Prasad, K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Circulation 1999, 99(10): 1355.

3. Rickard, S.E. and Thompson, L.U. Chronic exposure to secoisolariciresinol diglycoside alters lignan disposition in rats. J Nutr 1998, 128(3): 615.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

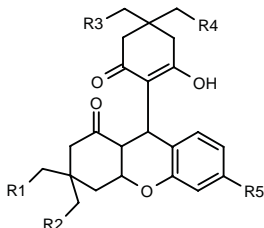
276099

9'-(6-Hydroxy-8-oxospiro[3.5]nona-6-en-7-yl)-2',3',4',9'-tetrahydro-1'H-spiro[cyclobutane-1,3'-xanthen]-1'-one



C₂₅ H₂₆ O₄; Mol wt: 390.4764

ACTION – A potent and selective neuropeptide Y (NPY) Y₅ receptor antagonist with an IC₅₀ value of 14 nM for inhibition of [¹²⁵I]-PYY binding to human Y₅ receptors. Potentially useful for the treatment of obesity, diabetes, bulimia, depression, epilepsy, hypertension, renal disorders, vascular spasm and dementia. Other compounds from this series of xanthen-1-one derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
276100	H	H	H	H	OMe	C ₂₄ H ₃₀ O ₅
276101	Me	Me	Me	Me	H	C ₂₇ H ₃₆ O ₄

SOURCE – Banyu.

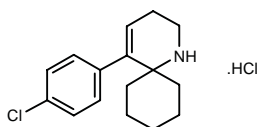
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BTS-71091*

211338

5-(4-Chlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride



C₁₆ H₂₀ Cl N . HCl; Mol wt: 298.2549

ACTION – Potent monoamine reuptake inhibitor proven to reduce food intake in rats (ED₅₀ = 15 mg/kg p.o.) by reducing the duration and frequency of eating episodes and to advance the onset and increase the duration of resting. The effect of compound on food intake is consistent with enhancement of the natural development of satiety.

SOURCE – Knoll.

REFERENCES

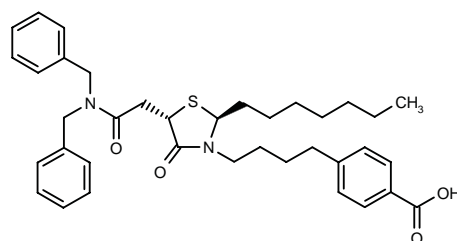
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*Identified compound **211338** Drug Data Report 1994, 016(10): 0889.

GW-0072

276278

(±)-(2*S**,5*S**)-4-[4-[5-[2-(Dibenzylamino)-2-oxoethyl]-2-heptyl-4-oxothiazolidin-3-yl]butyl]benzoic acid



C₃₇ H₄₆ N₂ O₄ S; Mol wt: 614.8464

White solid, m.p. 94-7 °C.

ACTION – High-affinity ligand for the peroxisome proliferator-activated receptor γ (PPARγ; K_i = 70 nM) with weak partial agonist activity, as demonstrated in a PPARγ transactivation assay. Compound was unable to convert multipotential stem cells into adipocytes and at 10 μM it showed potent inhibition of rosiglitazone-induced adipocyte differentiation. Potential new lead in the search for partial agonists for the treatment of metabolic diseases including diabetes and obesity.

SOURCES – Affymax; Glaxo Wellcome.

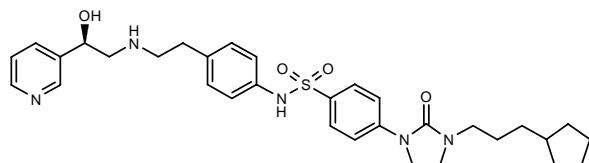
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L-766892

273701

4-[3-(3-Cyclopentylpropyl)-2-oxo-1-imidazolidinyl]-N-[4-[2-[2(*R*)-hydroxy-2-(3-pyridinyl)ethylamino]ethyl]phenyl]benzenesulfonamide



C32 H41 N5 O4 S; Mol wt: 591.7729

ACTION – Potent β_3 -adrenoceptor agonist ($EC_{50} = 5.7$ nM for stimulation of cAMP in CHO cells expressing the human receptor; 64% of the maximal activity of isoproterenol) with 420- and 130-fold selectivity over β_1 - and β_2 -adrenoceptors, respectively ($IC_{50} = 200$ and 760 nM, respectively, in binding assays). Compound showed moderate (17%) bioavailability in dogs. In anesthetized monkeys, it elicited hyperglycerolemia with an ED_{50} of 0.1 mg/kg i.v., without inducing significant changes in heart rate at doses up to 30 mg/kg. Potentially useful for the treatment of type II diabetes and obesity.

SOURCE – Merck & Co.

REFERENCES

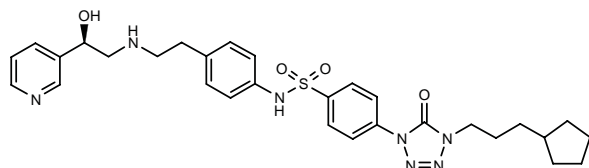
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2. Naylor, E.M. et al. *Human β_3 adrenergic receptor agonists containing imidazolidinone and imidazolone benzenesulfonamides*. Bioorg Med Chem Lett 1999, 9(5): 755.

L-770644

276070

4-[4-(3-Cyclopentylpropyl)-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl]-N-[4-[2-[2(*R*)-hydroxy-2-(3-pyridinyl)ethylamino]ethyl]phenyl]benzenesulfonamide



C30 H37 N7 O4 S; Mol wt: 591.7333

ACTION – Potent and selective human β_3 -adrenoceptor agonist ($EC_{50} = 13$ nM for stimulating adenylyl cyclase in CHO cells expressing cloned human β_3 -adrenoceptors) with 37- and 17-fold selectivity over β_1 - and β_2 -adrenoceptors, respectively. Compound showed high binding affinity for the human β_3 -adrenoceptor ($IC_{50} = 92$ nM) and good oral bioavailability (27%) in rats. It evoked hyperglycerolemia in dogs (10 mg/kg p.o.) and monkeys ($ED_{50} = 0.21$ mg/kg i.v.), where it elicited a maximum response equivalent to that of the full agonist isoproterenol, with minimal increase in heart rate.

SOURCE – Merck & Co.

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1. Fisher, M.H. et al. (Merck & Co., Inc.) *Substd. sulfonamides as selective β_3 agonists for the treatment of diabetes and obesity*. EP 757674, JP 97512275, US 5541197, US 5561142, WO 9529159.

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3. Smith, R.G. et al. (Merck & Co., Inc.) *Combination therapy for the treatment of diabetes and obesity*. WO 9818481.

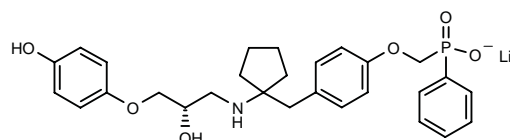
4. Shih, T.L. et al. *L-770,644: A potent and selective human β_3 adrenergic receptor agonist with improved oral bioavailability*. Bioorg Med Chem Lett 1999, 9(9): 1251.

SB-251023*

275312

266522 (as free acid)

4-[4-[2(*S*)-Hydroxy-3-[3-(4-hydroxyphenoxy)propylamino]cyclopentylmethyl]phenoxy]methyl(phenyl)phosphonic acid lithium salt



C28 H33 Li N O6 P; Mol wt: 517.4847

ACTION – Potent and selective human β_3 -adrenoceptor agonist proven to stimulate adenylyl cyclase activity in CHO cells expressing the human cloned β_3 -adrenoceptor ($pD_2 = 6.25$; intrinsic activity [IA] relative to isoprenaline = 0.66) and human white adipocyte lipolysis ($pD_2 = 6.19$; IA = 0.45 at 10 μ M); compound exhibited low affinity for β_1 - and β_2 -adrenoceptors ($pK_i = 3.91$ and 4.37, respectively). It did not stimulate atrial contractility or antagonize β_4 -adrenoceptor-mediated effects, but it did display non- β_3 -adrenoceptor-mediated cardiodepressant activity ($pD_2 = 6.49$). Potentially useful for the treatment of obesity and diabetes.

SOURCE – SmithKline Beecham.

REFERENCES

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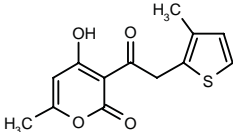
2. Arch, J.R.S. et al. *Studies on a novel selective β_3 -adrenoceptor agonist in human right atrial appendage and human white adipocytes*. Br J Pharmacol 1999, 126(Suppl.): Abst 100P.

*Identified compound 266522 (see 265525) Drug Data Report 1998, 020(08): 0729.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

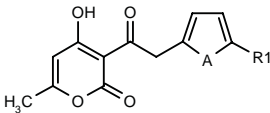
276219

4-Hydroxy-6-methyl-3-[2-(3-methylthien-2-yl)acetyl]-2H-pyran-2-one



C13 H12 O4 S; Mol wt: 264.2998

ACTION – Hematopoietic agent that promotes the production of platelets, leukocytes and erythrocytes and is therefore potentially useful for cancer chemotherapy or radiotherapy. It promoted the proliferation of murine myeloblasts *in vitro* and increased erythrocyte counts *in vivo* in mice. Other exemplified cyclic ketone derivatives include the following:



Compound	R1	A	Formula
276220	Me	S	C ₁₃ H ₁₂ O ₄ S
276222	NO2	S	C ₁₂ H ₉ NO ₅ S
276223	Et	O	C ₁₄ H ₁₄ O ₅

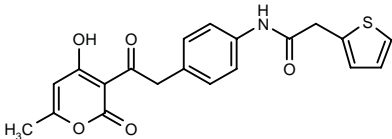
SOURCE – Toray.

REFERENCES

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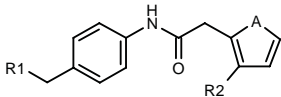
276358

N-[4-[2-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxoethyl]phenyl]-2-(thien-2-yl)acetamide

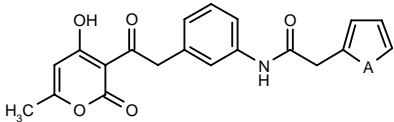


C20 H17 N O5 S; Mol wt: 383.4223

ACTION – Hematopoietic agent with the ability to promote the production of platelets, leukocytes and erythrocytes, and therefore useful in cancer chemotherapy, radiotherapy and bone marrow transplantation. Other representative ketone derivatives include the following:



Compound	R1	R2	A	Formula
276359	4-OH-6-Me-2-oxo-2H-pyran-3-yl-COCH2	H	S	C ₂₁ H ₁₉ NO ₅ S
276362	2-OH-6-oxo-1-cylohexenyl-CO	H	S	C ₂₀ H ₁₉ NO ₄ S
276364	4-OH-2-oxo-2H-1-benzopyran-3-yl-CO	H	S	C ₂₃ H ₁₇ NO ₅ S
276365	4-OH-6-Me-2-oxo-5,6-dihydro-2H-pyran-3-yl-CO	H	S	C ₂₀ H ₁₉ NO ₅ S
276366	4-OH-6-Me-2-oxo-2H-pyran-3-yl-CO	H	O	C ₂₀ H ₁₇ NO ₆
276368	4-OH-2-oxo-2,5-dihydro-2-furanyl-CO	H	S	C ₁₈ H ₁₅ NO ₅ S
276370	4-OH-6-Me-2-oxo-2H-pyran-3-yl-CO	Me	S	C ₂₁ H ₁₉ NO ₅ S



Compound	A	Formula
276360	S	C ₂₀ H ₁₇ NO ₅ S
276367	O	C ₂₀ H ₁₇ NO ₆

SOURCE – Toray.

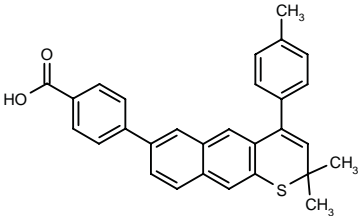
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TREATMENT OF POISONING, DRUG
ABUSE AND DEPENDENCY

273698

4-[2,2-Dimethyl-4-(4-methylphenyl)-2H-naphtho[2,3-b]-thiopyran-7-yl]benzoic acid



C29 H24 O2 S; Mol wt: 436.5726

ACTION – Retinoic acid receptor (RAR) antagonist that binds with high affinity to all three RAR subtypes ($K_d = 5.5, 6$ and 5 nM for RAR α , RAR β and RAR γ , respectively) without binding or transactivating retinoid X receptors (RXR). In functional studies compound showed full antagonist activity in suppressing the transactivation of RAR subtypes by TTNPB ($IC_{50} = 0.5-2$ nM). In mice, it was effective in reducing TTNPB-induced mucocutaneous toxicity. Potentially useful as an antidote for retinoid toxicity, as well as for the treatment of diseases involving RAR activation.

SOURCE – Allergan.

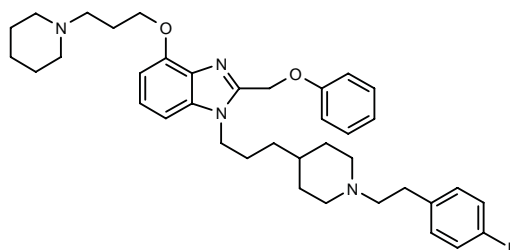
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PHARMACOLOGICAL TOOLS

273694

1-[3-[1-[2-(4-Iodophenyl)ethyl]piperidin-4-yl]propyl]-2-(phoxymethyl)-4-[3-(1-piperidinyl)propoxy]-1*H*-benzimidazole



C38 H49 I N4 O2; Mol wt: 720.7311

ACTION – Highly potent and selective neuropeptide Y (NPY) receptor antagonist with high affinity for cloned human Y_1 receptors ($K_i = 0.052$ nM) and > 10,000-fold selectivity over human Y_2 , Y_4 and Y_5 receptors. Compound showed functional antagonist activity in the forskolin-stimulated cAMP assay in the SK-N-MC cell line ($K_i = 6$ nM). Potentially useful as a pharmacological tool for elucidating the pathophysiological role of Y_1 receptors.

SOURCE – Lilly.

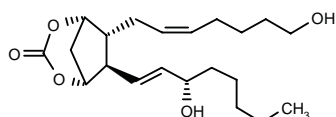
REFERENCES

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AGN-192093*

226109

1-Deoxyprostaglandin $F_{2\alpha}$ 9,11-*O*-cyclic carbonate



C21 H34 O5; Mol wt: 366.5020

ACTION – TxA_2 receptor agonist, a $PGF_{2\alpha}$ derivative shown to interact with thromboxane (TP) receptors in rat vascular smooth muscle but not in human platelets. Compound strongly contracted isolated rat thoracic aorta tissue ($EC_{50} = 1.3$ nM) and human myometrial smooth muscle strips, but had no effect (up to 10 μ M) on TP-modulated human platelet aggregation or on cloned

placental and endothelial TP receptors. Potentially useful as a pharmacological tool for distinguishing different TP receptor populations.

SOURCE – Allergan.

REFERENCES

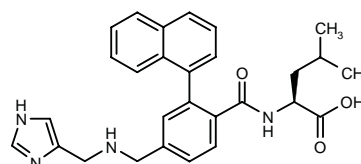
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*Identified compound **226109** (see **224970**) Drug Data Report 1995, 017(10): 0956.

GGTI-2151

275786

N-[4-(1*H*-Imidazol-4-yl)methylaminomethyl]-2-(1-naphthyl)benzoyl]-L-leucine



C28 H30 N4 O3; Mol wt: 470.5700

ACTION – Peptidomimetic, non-thiol-containing protein geranylgeranyltransferase I (GGTase-I) inhibitor ($IC_{50} = 44$ nM) with high selectivity over protein farnesyltransferase ($IC_{50} > 10,000$ nM). Potentially useful as a pharmacological tool to elucidate the effect of protein geranylgeranylation on normal and oncogenic cell growth, and also as a lead in the development of novel therapies for cancer and cardiovascular diseases.

SOURCES – University of Pittsburgh, Pittsburgh, PA (US); University of South Florida, Tampa, FL (US); Yale University, New Haven, CT (US).

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1. Vasudevan, A. et al. *Potent, highly selective, and non-thiol inhibitors of protein geranylgeranyltransferase-I.* J Med Chem 1999, 42(8): 1333.

SOURCE – Allergan.

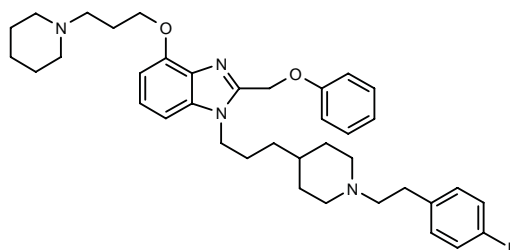
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PHARMACOLOGICAL TOOLS

273694

1-[3-[1-[2-(4-Iodophenyl)ethyl]piperidin-4-yl]propyl]-2-(phoxymethyl)-4-[3-(1-piperidinyl)propoxy]-1*H*-benzimidazole



C38 H49 I N4 O2; Mol wt: 720.7311

ACTION – Highly potent and selective neuropeptide Y (NPY) receptor antagonist with high affinity for cloned human Y_1 receptors ($K_i = 0.052$ nM) and > 10,000-fold selectivity over human Y_2 , Y_4 and Y_5 receptors. Compound showed functional antagonist activity in the forskolin-stimulated cAMP assay in the SK-N-MC cell line ($K_i = 6$ nM). Potentially useful as a pharmacological tool for elucidating the pathophysiological role of Y_1 receptors.

SOURCE – Lilly.

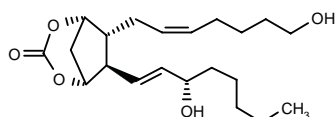
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AGN-192093*

226109

1-Deoxyprostaglandin $F_{2\alpha}$ 9,11-*O*-cyclic carbonate



C21 H34 O5; Mol wt: 366.5020

ACTION – TxA_2 receptor agonist, a $PGF_{2\alpha}$ derivative shown to interact with thromboxane (TP) receptors in rat vascular smooth muscle but not in human platelets. Compound strongly contracted isolated rat thoracic aorta tissue ($EC_{50} = 1.3$ nM) and human myometrial smooth muscle strips, but had no effect (up to 10 μ M) on TP-modulated human platelet aggregation or on cloned

placental and endothelial TP receptors. Potentially useful as a pharmacological tool for distinguishing different TP receptor populations.

SOURCE – Allergan.

REFERENCES

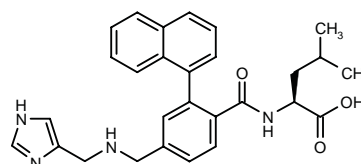
1. Burk, R.M. et al. (Allergan, Inc.) *7-[Carboxyalkyl or alkenyl]-6-[alkyl or alkenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]octane and derivs. thereof.* EP 737185, JP 97507229, US 5416106, WO 9518103.
2. Abbas, F. et al. *A comparative study of thromboxane (TP) receptor mimetics and antagonists on isolated human umbilical artery and myometrium.* Adv Exp Med Biol 1997, 407: 219.
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*Identified compound **226109** (see **224970**) Drug Data Report 1995, 017(10): 0956.

GGTI-2151

275786

N-[4-(1*H*-Imidazol-4-yl)methylaminomethyl]-2-(1-naphthyl)benzoyl]-L-leucine



C28 H30 N4 O3; Mol wt: 470.5700

ACTION – Peptidomimetic, non-thiol-containing protein geranylgeranyltransferase I (GGTase-I) inhibitor ($IC_{50} = 44$ nM) with high selectivity over protein farnesyltransferase ($IC_{50} > 10,000$ nM). Potentially useful as a pharmacological tool to elucidate the effect of protein geranylgeranylation on normal and oncogenic cell growth, and also as a lead in the development of novel therapies for cancer and cardiovascular diseases.

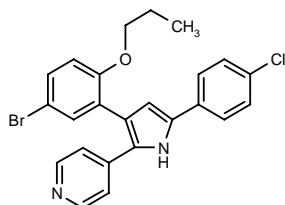
SOURCES – University of Pittsburgh, Pittsburgh, PA (US); University of South Florida, Tampa, FL (US); Yale University, New Haven, CT (US).

REFERENCES

1. Vasudevan, A. et al. *Potent, highly selective, and non-thiol inhibitors of protein geranylgeranyltransferase-I.* J Med Chem 1999, 42(8): 1333.

L-168049***267578**

4-[3-(5-Bromo-2-propoxyphenyl)-5-(4-chlorophenyl)-1H-pyrrol-2-yl]pyridine



C₂₄ H₂₀ Br Cl N₂ O; Mol wt: 467.7920

ACTION – Glucagon receptor (GLUR) antagonist with high affinity for human (IC₅₀ = 0.17 μM in the presence of Mg²⁺; IC₅₀ = 0.007 μM in the absence of Mg²⁺) and mouse glucagon receptors (IC₅₀ = 0.25 μM in the presence of Mg²⁺; IC₅₀ = 0.037 μM in the absence of Mg²⁺) in transfected CHO cells. Compound showed noncompetitive functional antagonist activity by inhibiting glucagon-stimulated cAMP synthesis in CHO cells expressing hGLUR (IC₅₀ = 41 nM; K_b = 25 nM) and was inactive as a GLUR agonist since it could not stimulate cAMP in murine liver membranes at up to 10 μM. It showed good oral bioavailability in rats and mice. Reduced inhibitory activity against p38 was observed relative to SB-203580 (IC₅₀ = 1.44 μM vs. 0.037 μM). Potentially useful as a tool to elucidate the therapeutic relevance of glucagon inhibition in animal models of diabetes.

SOURCE – Merck & Co.

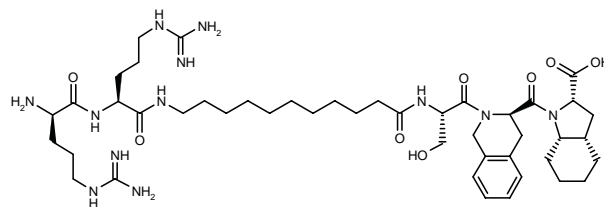
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3. de Laszlo, S.E. et al. *Potent, orally absorbed glucagon receptor antagonists*. Bioorg Med Chem Lett 1999, 9(5): 641.
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*Identified compound **267578** Drug Data Report 1998, 020(10): 0867.

MEN-11575**273107**

(2S,3aS,7aS)-1-[2-[11-(D-Arginyl-L-arginylamino)-undecanoyl-L-seryl]-1,2,3,4-tetrahydroisoquinolin-3(R)-ylcarbonyl]perhydroindole-2-carboxylic acid



C₄₅ H₇₄ N₁₂ O₈; Mol wt: 911.1556

ACTION – Bradykinin B₁ receptor antagonist, a pseudopeptide with high selectivity for B₁ receptors (pA₂ = 7.1 in rat ileum smooth muscle) over B₂ receptors (inactive at up to 10 μM in guinea pig ileum smooth muscle). It is considered a lead compound for the development of new peptidomimetic kinin antagonists as potential tools for the treatment of bradykinin B₁-mediated tissue damage and inflammatory processes.

SOURCE – Menarini.

REFERENCES

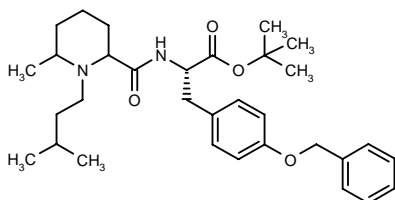
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ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

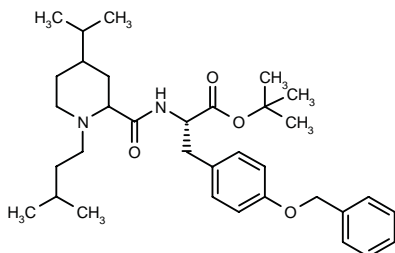
274146

N-[6-Methyl-1-(3-methylbutyl)piperidin-2-ylcarbonyl]-4-*O*-(benzyl)-*L*-tyrosine *tert*-butyl ester



C32 H46 N2 O4; Mol wt: 522.7254

ACTION – N-type calcium channel blocker, an analogue of PD-175069 with an IC_{50} value of 0.32 μ M for blockade of calcium flux through the N-type calcium channel in human neuroblastoma IMR-32 cells. Potentially useful for the treatment of neuronal injury or cerebral ischemia and chronic intractable pain. Another related compound is:



274147: C34 H50 N2 O4

SOURCES – Elan; Warner-Lambert.

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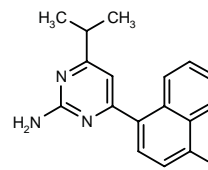
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- Hu, L.-Y. et al. Synthesis and biological evaluation of substituted 4-(OBz)phenylalanine derivatives as novel N-type calcium channel blockers. Bioorg Med Chem Lett 1999, 9(8): 1121.

ANTIMIGRAINE DRUGS

RS-127445*

259044

4-(4-Fluoro-1-naphthyl)-6-isopropylpyrimidin-2-amine



C17 H16 F N3; Mol wt: 281.3324

ACTION – Potent, selective and orally active 5-HT receptor antagonist with high selectivity for 5-HT_{2B} receptors (pK_i = 9.5) versus 5-HT_{2A} and 5-HT_{2C} receptors (pK_i < 6.0). In HEK-293 cells expressing human 5-HT_{2B} receptors, compound blocked 5-HT-induced inositol phosphate formation (pK_B = 9.5) and 5-HT-mediated increases in intracellular calcium (pIC_{50} = 10.4). Compound was also able to antagonize 5-HT-induced rat stomach fundus contractions (pA_2 = 9.5) and 5-HT_{2B} like receptor-mediated, endothelium-dependent rat jugular vein relaxation (pA_2 = 9.9). It showed a favorable pharmacokinetic profile, with oral and i.p. bioavailabilities of 14 and 60%, respectively. In anesthetized rats, RS-127445 (1 or 2.5 mg/kg i.p.) inhibited dura mater plasma protein extravasation induced by the 5-HT_{2B/2C} receptor antagonist mCPP and it attenuated (30 and 41%, respectively, at doses of 2 and 5 mg/kg i.v.) the capsaicin-evoked expression of c-fos protein in the cervical trigeminal nucleus caudalis. Potentially useful for the treatment of migraine.

SOURCE – Roche Bioscience.

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*Identified compound **259044** Drug Data Report 1998, 020(03): 0200.

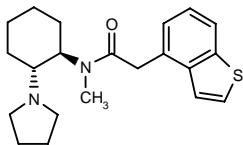
ANESTHETIC DRUGS

RSD-921

236882

(+)-(1*R*,2*R*)-*N*-Methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[*b*]thiophene-4-acetamide

PD-123497



C21 H28 N2 O S; Mol wt: 356.5312

ACTION – Local anesthetic and class I antiarrhythmic agent, an Na⁺ channel-blocking agent able to block all three wild-type channel isoforms, i.e., heart, skeletal muscle and neuronal isoforms (EC₅₀ = 47, 35 and 37 μM, respectively), as well as the IFMQ3 mutant channel (EC₅₀ = 110 μM). Compound interacts with the open state of the Na⁺ channel to produce use-dependent block. It may exert potent local anesthetic or antiarrhythmic effects under shortened action potentials, such as during anoxia or ischemia. Phase II trials in the latter indication have been completed.

SOURCES – Chemical Company of Malaysia; Nortran; Warner-Lambert.

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2. MacLeod, B.A. et al. (University of British Columbia) *Aminocyclohexylamides for antiarrhythmic and anaesthetic uses*. EP 632806, JP 95505151, WO 9319056.

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6. Pugsley, M.K. and Goldin, A.L. *Molecular analysis of the Na⁺ channel blocking actions of the novel class I anti-arrhythmic agent RSD 921*. Br J Pharmacol 1999, 127(1): 9.

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11. *Nortran completes phase II trial of RSD-921*. DailyDrugNews.com (Daily Essentials) 1998, Sept 22.

12. *Nortran exercises option on Parke-Davis compounds*. Nortran Pharmaceuticals Inc. Press Release 1996, Jan 19.

13. *Nortran initiates phase II trials for local anesthetic*. DailyDrugNews.com (Daily Essentials) 1998, July 23.

14. *Nortran Pharmaceuticals Inc.. Innovative Drug Develop '96: Companies, Technol Opportunities* (March 18-19, New York) 1996.

15. *Nortran updates patent status*. Nortran Pharmaceuticals Inc. Press Release 1995, Nov 7.

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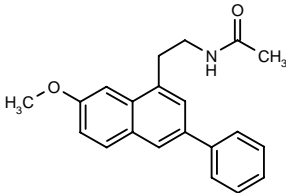
19. *RSD 921 to enter clinical trials*. Nortran Pharmaceuticals Inc. Press Release 1996, Feb 13.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

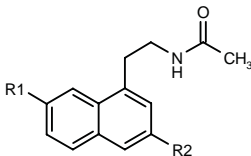
277285

N-[2-(7-Methoxy-3-phenyl-1-naphthyl)ethyl]acetamide



C21 H21 N O2; Mol wt: 319.4019

ACTION – Agent with strong affinity for melatonin receptors, particularly useful for the treatment of sleep disorders, seasonal depression, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. Other specifically claimed compounds from this series of naphthalene derivatives include the following:



Compound	R1	R2	Formula
277286	OMe	3-CF3-Ph	C ₂₂ H ₂₀ F ₃ NO ₂
277287	OMe	3-NH2-Ph	C ₂₁ H ₂₂ N ₂ O ₂
277288	OMe	2-furyl	C ₁₉ H ₁₉ NO ₃
277289	OMe	4-Pyr	C ₂₀ H ₂₀ N ₂ O ₂
277297	Ph	H	C ₂₀ H ₁₉ NO
277298	4-Me-Ph	H	C ₂₁ H ₂₁ NO

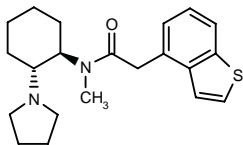
ANESTHETIC DRUGS

RSD-921

236882

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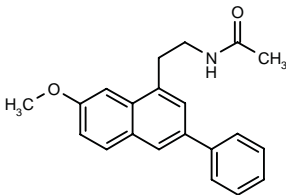
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

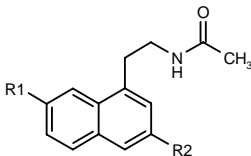
277285

N-[2-(7-Methoxy-3-phenyl-1-naphthyl)ethyl]acetamide

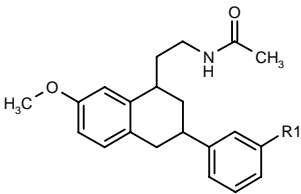


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277288	OMe	2-furyl	C ₁₉ H ₁₉ NO ₃
277289	OMe	4-Pyr	C ₂₀ H ₂₀ N ₂ O ₂
277297	Ph	H	C ₂₀ H ₁₉ NO
277298	4-Me-Ph	H	C ₂₁ H ₂₁ NO



Compound	R1	Formula
277300	H	C ₂₁ H ₂₅ NO ₂
277301	CF3	C ₂₂ H ₂₄ F ₃ NO ₂

SOURCE – ADIR.

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ZALEPLON+

Rec INN; USAN

132769

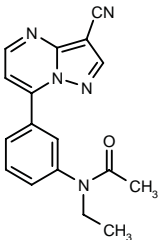
3'-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)-N-ethylacet-anilide

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide

CL-284846

L-846

LJC-10846



C17 H15 N5 O; Mol wt: 305.3395

ACTION – Pyrazolopyrimidine hypnotic structurally different from the benzodiazepines that selectively binds to the benzodiazepine type 1 receptor.

INDICATION – Treatment of severe, disabling or extremely distressing insomnia for a maximum of 2 weeks.

PRESENTATION – Capsules, 5 and 10 mg.

PROPRIETARY NAME – Sonata (DE, DK, SE).

SOURCE – Wyeth-Ayerst.

RECENT REFERENCES

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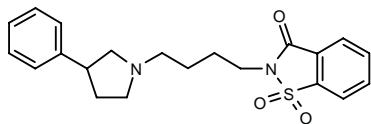
MONOGRAPH – Mealy, N. and Castañer, J. *Zaleplon*. Drugs Fut 1996, 21(1): 0037.

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ANXIOLYTICS

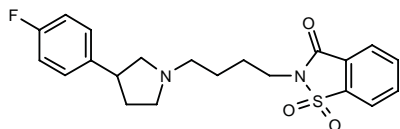
277032

2-[4-(3-Phenylpyrrolidin-1-yl)butyl]-1*H*-benzothiazol-3(2*H*)-one 1,1-dioxide



C₂₁ H₂₄ N₂ O₃ S; Mol wt: 384.4976

ACTION – Potent 5-HT_{1A} receptor ligand ($K_i = 2.7$ nM against [³H]-8-OH-DPAT binding in rat hippocampus) with some selectivity over 5-HT_{2A} receptors and α_2 -adrenoceptors ($K_i = 34$ and 16 nM, respectively) and high selectivity over dopamine D₁ and D₂ receptors ($K_i = 12,502$ and 195 nM, respectively). Compound was active *in vivo* in animal tests predictive for anxiolytic or anti-depressant activity, such as the corticosterone secretion test, the body temperature change test, the forced swimming test, the face-to-face test and the isolation-induced aggression test. Potentially useful for the treatment of mood and anxiety disorders. Another related *N*-substituted-3-arylpyrrolidine is:



277033: C₂₁ H₂₃ F N₂ O₃ S

SOURCE – LG Chemical.

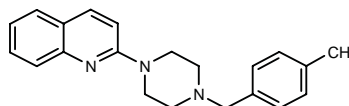
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ANTIPSYCHOTIC DRUGS

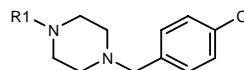
276038

2-[4-(4-Methylbenzyl)piperazin-1-yl]quinoline



C₂₁ H₂₃ N₃; Mol wt: 317.4337

ACTION – Antipsychotic agent, a selective dopamine D₄ receptor antagonist reported to be devoid of the side effects of conventional (nonselective) neuroleptics. It gave a K_i value of 8 nM when tested for its D₄ receptor affinity, whereas the K_i value against D₂ receptors was > 4000 nM. Other representative compounds within this series of piperazine derivatives include the following:



Compound	R1	Formula
276039	2-quinoxaliny	C ₁₉ H ₁₉ ClN ₄
276040	2-Naph	C ₂₁ H ₂₁ ClN ₂
276041	5,6,7,8-tetrahydro-2-quinoliny	C ₂₀ H ₂₄ ClN ₃

SOURCES – Neurogen; Schering-Plough.

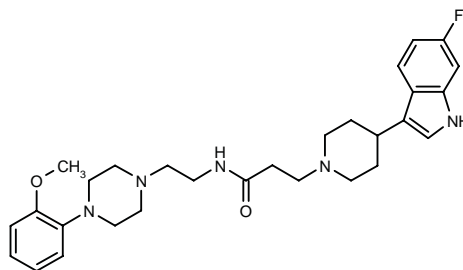
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TREATMENT FOR MOOD DISORDERS

276042

3-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]-*N*-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]propionamide



C₂₉ H₃₈ F N₅ O₂; Mol wt: 507.6502

ACTION – Dual 5-HT reuptake inhibitor and 5-HT_{1D} receptor antagonist with potential in the treatment of a broad range of disorders including depression, anxiety, obsessive-compulsive disorder, obesity, migraine, pain, bulimia, alcoholism, tobacco abuse, sleep disorders, dementia, Parkinson's disease and sexual dysfunction. A specifically claimed compound within a series of arylpiperazine derivatives.

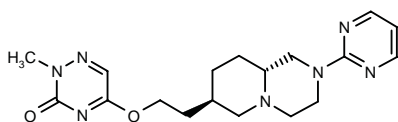
SOURCE – Lilly.

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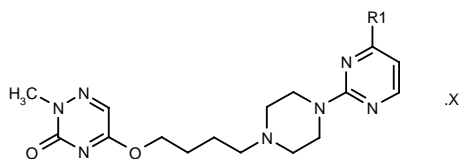
276044

(+)-*trans*-5-[2-[2-(Pyrimidin-2-yl)perhydropyrido[1,2-*a*]-pyrazin-7-yl]ethoxy]-2-methyl-1,2,4-triazin-3(2*H*)-one

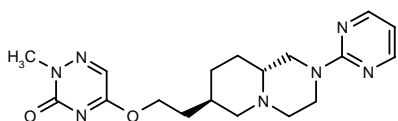


C₁₈ H₂₅ N₇ O₂; Mol wt: 371.4425

ACTION – Highly potent and selective 5-HT_{1A} receptor ligand (pK_i = 9.61) with improved affinity compared to buspirone (pK_i = 7.65) and flesinoxan (pK_i = 8.91); 5-HT_{1A} receptor-agonist activity was assessed *in vivo* by measuring reciprocal forepaw treading, lower lip retraction and flat-body posture in rats upon p.o. administration, with ED₅₀ values of < 0.04, < 0.04 and 0.04 mg/kg, respectively, compared to respective ED₅₀ values of 20, 2.5 and > 40 mg/kg p.o. for buspirone and 1.25, 1.25 and 5 mg/kg p.o. for flesinoxan. Antidepressant activity was shown *in vivo* in the forced swimming test (ED₅₀ = 0.04 mg/kg p.o.). Potentially useful for the treatment of depression, anxiety, pain, neurodegeneration, schizophrenia, Alzheimer's disease, sleep disturbances, eating disorders, cerebrovascular and cardiovascular disorders and vomiting. Within this series of 1,2,4-triazin-3(2*H*)-one derivatives, the following are also included:



Compound	R1	X	Formula
276045	Me	fumarate	C ₁₇ H ₂₅ N ₇ O ₂ ·C ₄ H ₄ O ₄
276046	Cl		C ₁₆ H ₂₂ ClN ₇ O ₂



276047: C₁₈ H₂₅ N₇ O₂

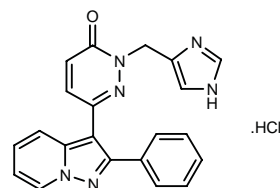
SOURCE – Pierre Fabre.

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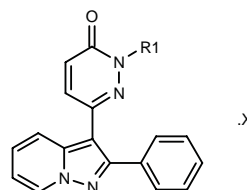
276402

2-(1*H*-Imidazol-4-ylmethyl)-6-(2-phenylpyrazolo[1,5-*a*]-pyridin-3-yl)-2,3-dihydropyridazin-3-one hydrochloride



C₂₁ H₁₆ N₆ O . HCl; Mol wt: 404.8593

ACTION – Adenosine A₁ receptor antagonist, as demonstrated in a binding assay by > 90% inhibition of [³H]-DPCPX binding to human A₁ receptors at 0.1 μM. Potentially useful for the treatment or prevention of a broad range of disorders including depression, dementia, anxiety, pain, stroke, hypertension, edema, and heart and renal failure. A representative compound from a series of pyrazolopyridine derivatives, wherein the following are also included:



Compound	R1	X	Formula
276613	2-Pyr-CH ₂	HCl	C ₂₃ H ₁₉ N ₅ O·HCl
276614	CH ₂ C(Me) ₂ OH		C ₂₁ H ₂₂ N ₄ O ₂
276615	4-pyrazolyl-CH ₂ CH ₂	HCl	C ₂₂ H ₂₀ N ₆ O·HCl
276616	CH ₂ CH ₂ N(Me)Ac		C ₂₂ H ₂₃ N ₅ O ₂
276617	CH ₂ CH(Me)N(Me)CH ₂ Ph		C ₂₈ H ₂₉ N ₅ O

SOURCE – Fujisawa.

REFERENCES

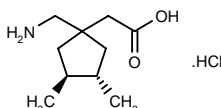
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

276472

(+)-*trans*-2-(1-Aminomethyl-3,4-dimethylcyclopentyl)-acetic acid hydrochloride



C10 H19 N O2 . HCl; Mol wt: 221.7260

ACTION – Agent for the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic disorders, pain, inflammation and gastrointestinal disorders, an analogue of gabapentin with higher binding affinity for the Ca^{2+} channel $\alpha 2\text{-}\delta$ subunit ($\text{IC}_{50} = 0.022 \mu\text{M}$ against $[^3\text{H}]$ -gabapentin binding to the $\alpha 2\text{-}\delta$ subunit derived from porcine brain tissue vs. $0.10\text{-}0.12 \mu\text{M}$ for gabapentin). Compound exhibited anticonvulsant properties in an audiogenic seizure model in mice, where it completely protected animals from sound-induced tonic seizures at 30 mg/kg p.o. A representative compound from a series of cyclic amino acid derivatives.

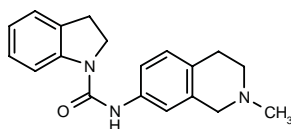
SOURCE – Warner-Lambert.

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276959

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2,3-dihydro-1*H*-indole-1-carboxamide



C19 H21 N3 O; Mol wt: 307.3949

ACTION – Anticonvulsant also reported to be useful in the treatment or prevention of anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, Alzheimer's disease, Parkinson's disease, sleep disorders and traumatic brain injury. Compound exhibits high affinity for the $[^3\text{H}]$ -SB-204269 binding site in rat forebrain membranes ($\text{pK}_i > 8$). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) test in mice, where it gave a 225% increase in seizure threshold at 2 mg/kg p.o. A representative compound from a series of isoquinoline derivatives.

SOURCE – SmithKline Beecham.

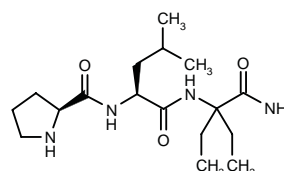
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

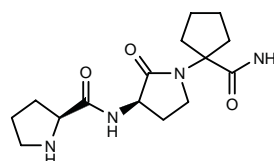
276011

L-Prolyl-L-leucyl-2,2-(diethyl)glycinamide



C17 H32 N4 O3; Mol wt: 340.4648

ACTION – Peptidomimetic dopamine receptor modulator proven to enhance apomorphine-induced rotational behavior in 6-OHDA-lesioned rats (56% at $1 \mu\text{g/kg i.p.}$) and to increase the binding of the agonist $[^3\text{H}]$ -*N*-propylnorapomorphine to dopamine D_2 receptors (40% at $0.1 \mu\text{M}$), as well as to decrease haloperidol-induced catalepsy in rats. Potentially useful for the treatment of extrapyramidal motor disorders and depression. Within this series of L-prolyl-L-leucyl-glycinamide peptidomimetics, the following is also included:



275794: C15 H24 N4 O3

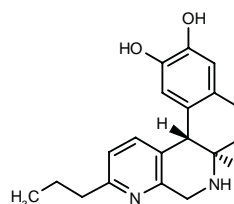
SOURCES – McMaster University, Hamilton, ON (CA); University of Minnesota, Minneapolis, MN (US).

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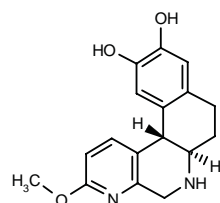
277030

trans-3-Propyl-5,6,6a,7,8,12b-hexahydronaphtho[1,2-*f*]-[1,7]naphthyridine-10,11-diol



C19 H22 N2 O2; Mol wt: 310.3948

ACTION – High-affinity dopamine D₁ receptor ligand (K_i = 45 nM) with high selectivity over D₂ receptors (K_i = 450 nM) and agonist activity in the adenylate cyclase functional assay (EC_{50} = 8.6 nM, 116% intrinsic activity relative to dopamine). Potentially useful for the treatment of dopamine-related CNS disorders such as Parkinson's disease, schizophrenia, drug abuse, eating disorders and depression. Another related compound is:



277029: C₁₇ H₁₈ N₂ O₃

SOURCE – Abbott.

REFERENCES

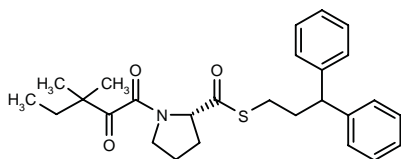
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2. Gu, Y.G. et al. *trans*-2,6-,3,6- And 4,6-diaza-5,6,6a,7,8,12b-hexahydrobenzo[c]phenanthrene-10,11-diols as dopamine agonists. Bioorg Med Chem Lett 1999, 9(10): 1341.

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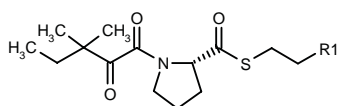
274132

1-(3,3-Dimethyl-2-oxopentanoyl)pyrrolidine-2(*S*)-carbothioic acid *S*-(3,3-diphenylpropyl) ester



C₂₇ H₃₃ N O₃ S; Mol wt: 451.6277

ACTION – Neuroprotective and neuroregenerative agent, a high-affinity ligand for the peptidyl-prolyl isomerase FKBP12 (K_i = 7 nM for inhibition FKBP12 enzymatic activity). *In vivo* in a model of Parkinson's disease (MPTP-induced neurodegeneration in mice), compound was able to block (56 and 69%, respectively, at 4 mg/kg s.c. and 10 mg/kg p.o.) the degeneration of dopaminergic neurons induced by MPTP and was effective in restoring striatal innervation when administered subsequent to lesioning with MPTP. Potentially useful for the treatment of neurodegenerative disorders. Other related compounds are:



Compound	R1	Formula
274133	Ph	C ₂₀ H ₂₇ NO ₃ S
274134	CH ₂ Ph	C ₂₁ H ₂₉ NO ₃ S
274135	3-Pyr-CH ₂	C ₂₀ H ₂₈ N ₂ O ₃ S
274136	4-MeO-PhCH ₂	C ₂₂ H ₃₁ NO ₄ S
274137	2-Naph-CH ₂	C ₂₅ H ₃₁ NO ₃ S

SOURCE – Guilford.

REFERENCES

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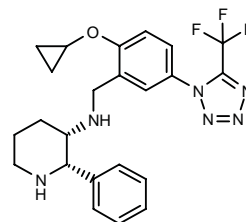
2. Hamilton, G.S. and Steiner, J.P. (Guilford Pharmaceuticals Inc.) *Hair growth compsns. and uses*. WO 9855090.

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TREATMENT OF NAUSEA AND VOMITING

276797

(2*S*,3*S*)-3-[2-Cyclopropoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]benzylamino]-2-phenylpiperidine



C₂₃ H₂₅ F₃ N₆ O; Mol wt: 458.4855

ACTION – Potent tachykinin, especially NK₁ (substance P), receptor antagonist that exhibits high hepatic stability, high oral bioavailability and an enhanced duration of action. It is reported to attenuate cisplatin-induced emesis in a ferret model. Particularly useful in the treatment of combined postoperative pain and postoperative nausea and vomiting, and emesis induced by cancer chemotherapy, other pharmacological agents or radiation.

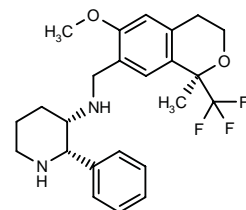
SOURCE – Merck Sharp & Dohme.

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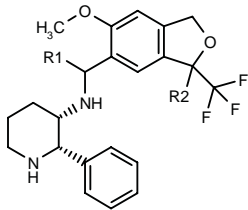
276940

(2*S*,3*S*)-3-[1(*R*)-Methyl-6-methoxy-1-(trifluoromethyl)-3,4-dihydro-1*H*-2-benzopyran-7-ylmethylamino]-2-phenylpiperidine



C₂₄ H₂₉ F₃ N₂ O₂; Mol wt: 434.4991

ACTION – A substance P (NK₁ receptor) antagonist reported to possess lower susceptibility to metabolism compared to structurally related compounds, particularly useful as an antiinflammatory and antiemetic agent and for the treatment of CNS disorders including depression, anxiety and cognitive disorders; it is preferably useful in the treatment of emesis induced by antineoplastic agents and other pharmacological agents such as rolipram or morphine. Other specifically claimed trifluoromethyl-substituted cyclic ether derivatives include the following:



Compound	R1	R2	Formula
276941	H	H	C ₂₂ H ₂₆ F ₃ N ₂ O ₂
276942	H	Me	C ₂₃ H ₂₇ F ₃ N ₂ O ₂
276944	H	Ph	C ₂₈ H ₂₉ F ₃ N ₂ O ₂
276945	Me	Me	C ₂₄ H ₂₈ F ₃ N ₂ O ₂

SOURCE – Pfizer.

REFERENCES

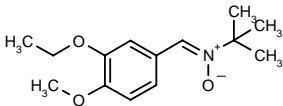
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COGNITION-ENHANCING DRUGS

276146

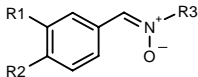
N-tert-Butyl-*N*-(3-ethoxy-4-methoxybenzylidene)amine *N*-oxide

N-tert-Butyl- α -(3-ethoxy-4-methoxyphenyl)nitron



C14 H21 N O3; Mol wt: 251.3239

ACTION – Agent for the treatment or prevention of neurodegenerative, autoimmune and inflammatory disorders, particularly Alzheimer’s disease, that acts by inhibiting the formation of amyloid β -peptide(1-42) β -pleated sheets and has been found to protect against neuronal cell loss and to inhibit the release of cytokines such as IL-1 β and tumor necrosis factor- α (TNF- α). *In vivo*, compound was found to be effective in the guinea pig myelin basic protein (MBP)-induced experimental allergic encephalomyelitis model in rats when given at a dose of 100 mg/kg p.o. Other exemplified compounds from this series of α -aryl-*N*-alkylnitrones include the following:



Compound	R1	R2	R3	Formula
276147	H	OEt	cyclohexyl	C ₁₅ H ₂₁ NO ₂
276148	OEt	OMe	i-Pr	C ₁₃ H ₁₉ NO ₃
276149	OEt	OC6H13	cyclohexyl	C ₂₁ H ₃₃ NO ₃
276150	H	OCH2Ph	t-Bu	C ₁₈ H ₂₁ NO ₂
276151	H	OCH2Ph	cyclopentyl	C ₁₉ H ₂₁ NO ₂
276152	OEt	OMe	t-BuCH2C(Me)2	C ₁₈ H ₂₉ NO ₃

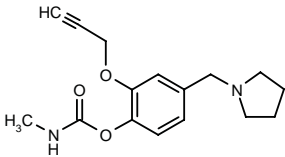
SOURCE – Centaur.

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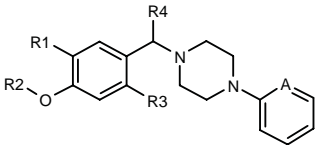
276423

N-Methylcarbamic acid 2-(2-propynyloxy)-4-(1-pyrrolidin-ylmethyl)phenyl ester

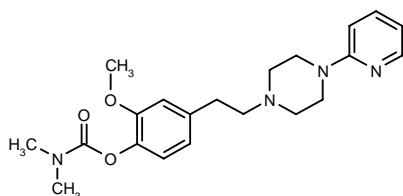


C16 H20 N2 O3; Mol wt: 288.3450

ACTION – Acetylcholinesterase inhibitor (IC₅₀ = 0.0036 μ M) with potential in the treatment of memory disorders, particularly those associated with decreased cholinergic activity such as in Alzheimer’s disease. Other compounds from this series of aminoalkylphenol derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
276424	ethynyl-CH2O	Me	H	H	N	C ₂₀ H ₂₃ N ₃ O ₂
276425	OMe	CONHMe	H	H	N	C ₁₉ H ₂₄ N ₄ O ₃
276426	OCNHMe	Me	H	H	N	C ₁₉ H ₂₄ N ₄ O ₃
276428	OMe	CONHMe	H	H	C(Me)	C ₂₁ H ₂₇ N ₃ O ₃
276430	OMe	CON(Me)2	Br	H	N	C ₂₀ H ₂₅ BrN ₄ O ₃
276434	OMe	CONHMe	H	H	C(F)	C ₂₀ H ₂₄ FN ₃ O ₃
276436	F	CON(Me)2	H	Me	N	C ₂₀ H ₂₅ FN ₄ O ₂
276437	OMe	CON(Me)2	H	Me	N	C ₂₁ H ₂₈ N ₄ O ₃



276433: C₂₁ H₂₈ N₄ O₃

Some compounds within the invention are reported to be clonidine binding inhibitors and are useful as antidepressants.

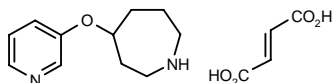
SOURCE – Hoechst Marion Roussel.

REFERENCES

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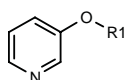
276832

4-(3-Pyridinyloxy)perhydroazepine fumarate



C₁₁ H₁₆ N₂ O . C₄ H₄ O₄; Mol wt: 308.3320

ACTION – Nicotinic acetylcholine receptor (AChR) ligand giving IC₅₀ values for [³H]-cytisine (α4 and β2 subunits), [³H]-epibatidine (α4β2 subtype) and [³H]-α-bungarotoxin (α7 and α1 subunits) binding of 0.06, 0.30 and 20.0 μM, respectively. Expected to be useful in the treatment of conditions involving the cholinergic system including Alzheimer's disease and other cognitive and neurodegenerative disorders, withdrawal from tobacco and other addictive substances, pain, disorders associated with smooth muscle contraction and inflammatory disorders. Other aza-ring ether derivatives are:



Compound	R1	Formula
276833	1-Me-3-pyrrolidinyl	C ₁₀ H ₁₄ N ₂ O
276834	3-pyrrolidinyl	C ₉ H ₁₂ N ₂ O
276835	1-Me-3-Pip	C ₁₁ H ₁₆ N ₂ O

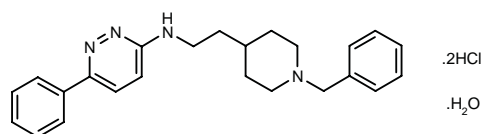
SOURCE – NeuroSearch.

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1. Peters, D. et al. (NeuroSearch A/S) *Azaring-ether derivs. and their use as nicotinic ACh receptor modulators.* WO 9924422.

277068

N-[2-(1-Benzyl-4-piperidiny)ethyl]-6-phenylpyridazin-3-amine dihydrochloride hydrate



C₂₄ H₂₈ N₄ . 2HCl . H₂O; Mol wt: 463.4498

M.p. 268 °C.

ACTION – Acetylcholinesterase (AChE) inhibitor with submicromolar activity against AChE from both electric eel and human erythrocytes (IC₅₀ = 0.12 and 0.14 μM, respectively) and 5-fold selectivity over butyrylcholinesterase (BuChE; IC₅₀ = 0.70 μM). Compound was at least as potent and about 10-fold more selective for AChE over BuChE than tacrine, whereas it was less potent and considerably less selective than donepezil. In comparison to the parent compound minaprine, this new AChE inhibitor showed a 5000-fold increase in potency. Potentially useful for the treatment of CNS diseases related to a deficit in cholinergic neurotransmission such as Alzheimer's disease.

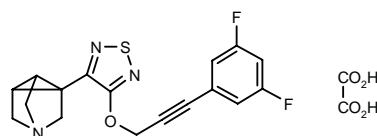
SOURCE – Université Louis Pasteur, Strasbourg (FR).

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277082

1-[4-[3-(3,5-Difluorophenyl)-2-propynyloxy]-1,2,5-thiadiazol-3-yl]-4-azatricyclo[2.2.1.0^{2,6}]heptane oxalate



C₁₇ H₁₃ F₂ N₃ O S . C₂ H₂ O₄; Mol wt: 435.4055

M.p. 173-5 °C.

ACTION – High-affinity muscarinic M₁ receptor ligand (IC₅₀ = 30 nM for inhibition of [³H]-Oxo-M binding in rat brain membranes) with agonist activity in mouse fibroblast A9L cells expressing the M₁ receptor subtype (EC₅₀ = 20.2 nM for stimulation of phosphoinositol hydrolysis) and > 100-fold functional selectivity over the M₂ subtype (IC₅₀ = 2690 nM for inhibition of forskolin-induced cAMP formation in CHO cells expressing human M₂ receptors). Compound showed good oral bioavailability (20-30%) in rats and did not induce salivation or tremor in mice. Potentially useful for the treatment of CNS disorders caused by dysfunction of the muscarinic cholinergic system such as Alzheimer's disease.

SOURCES – Lilly; Novo Nordisk.

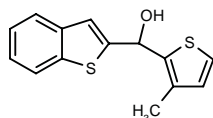
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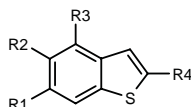
277375

1-(Benzo[b]thiophen-2-yl)-1-(3-methylthien-2-yl)methanol



C14 H12 O S2; Mol wt: 260.3798

ACTION – Agent for the treatment of Alzheimer's disease that acts by virtue of its ability to inhibit amyloid β -protein-induced neurotoxicity, as demonstrated *in vitro* in MTT assays using amyloid β (25-35) peptide in rat fetal hippocampal nerve cells and HeLa cells (66 and 71% inhibition at 10 μ g/ml), as well as amyloid β (1-40) peptide in HeLa cells (101% inhibition at 10 μ g/ml). Other exemplified compounds from this series of fused heterocyclic derivatives include the following:



Compound	R1	R2	R3	R4	Formula
277377	H	2-thienyl-CH2	OH	H	C ₁₃ H ₁₀ OS ₂
277378	H	Me	H	2-thienyl-CH(OH)	C ₁₄ H ₁₂ OS ₂
277381	Cl	H	H	5-Me-2-thienyl-CH(OH)	C ₁₄ H ₁₁ ClOS ₂
277384	H	2-thienyl-CH(OH)	H	H	C ₁₃ H ₁₀ OS ₂

SOURCE – Sankyo.

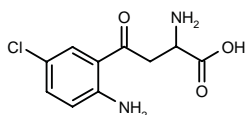
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FCE-27813

277271

2-Amino-4-(2-amino-5-chlorophenyl)-4-oxobutyric acid



C10 H11 Cl N2 O3; Mol wt: 242.6609

ACTION – Kynurenine aminotransferase (KAT) inhibitor potentially useful in the treatment or prevention of cognition disorders associated with aging processes of the brain, as well as of perinatal brain disorders. *In vitro*, compound was shown to inhibit KAT activity in rat brain homogenates (45 and 81% inhibition at 100 and 1000 μ M, respectively) and the production of kynurenic acid in rat cortical slices (63 and 84% inhibition at 100 and 1000 μ M, respectively).

SOURCES – University of Maryland, Baltimore, MD (US); Pharmacia & Upjohn.

REFERENCES

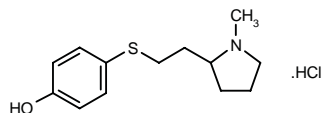
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SIB-1553A*

251678

252412 (as free base)

2-[2-(4-Hydroxyphenylsulfanyl)ethyl]-1-methylpyrrolidine hydrochloride



C13 H19 N O S . HCl; Mol wt: 273.8260

ACTION – Cognition-enhancing agent, a human neuronal nicotinic acetylcholine ion channel receptor (nAChR) agonist with selectivity for β 4 subunit-containing receptors, as demonstrated in human embryonic kidney cells stably expressing human β 4 subtypes and in *Xenopus* oocytes, where compound elicited inward currents and showed selectivity for α 4 β 4 subtype nAChRs; weak activity on α 3 β 4 and α 7 receptors was observed. Compound was able to displace [³H]-dopamine binding in rat striatal slices (IC₅₀ = 6.5 nM) and [³H]-norepinephrine binding in rat prefrontal cortical preparations and hippocampal slices (IC₅₀ = 0.6 and 0.2 nM, respectively); *in vivo*, it increased dopamine release in the striatum and acetylcholine release in prefrontal cortex and hippocampus. SIB-1553A was found to improve cognitive deficits induced by aging or cholinergic dysfunction in rodents and nonhuman primates, with a broader range of activity and greater efficacy when compared to nicotine or donepezil. Currently in phase II trials in patients with Alzheimer's disease.

SOURCES – Lilly; Sibia Neurosciences.

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2. Bontempi, B. et al. SIB-1553A, a novel nAChR agonist with cognitive enhancing properties in aged rodents and non-human primates: Effects on various memory forms. *Soc Neurosci Abstr* 1997, 23(Part 2): Abstr 477.15.

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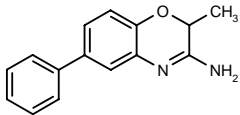
*Identified compound **252412** Drug Dara Rep 1997, 019(09): 0783.

TREATMENT OF

CEREBROVASCULAR DISEASES

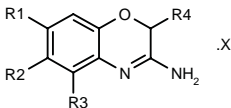
275235

2-Methyl-6-phenyl-2*H*-1,4-benzoxazin-3-amine



C15 H14 N2 O; Mol wt: 238.2886

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of neurodegenerative, inflammatory, autoimmune and cardiovascular disorders. Other specifically claimed compounds from this series of benzoxazine and benzothiazine derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
275236		-(CH2)3-	H	Me		C ₁₂ H ₁₄ N ₂ O
275237		-OCH2O-	H	Et		C ₁₁ H ₁₂ N ₂ O ₃
275238	H	-(CH2)4-		Me		C ₁₃ H ₁₆ N ₂ O
275239	H	2-thienyl-CH2NHCH2	H	Me	2HCl	C ₁₆ H ₁₇ N ₃ OS.2HCl
275240	H	3-MeO-PhCH2NHCH2	H	Me	2HCl	C ₁₈ H ₂₁ N ₃ O ₂ .2HCl
275241	H	4-MeSO2-PhCH2NHCH2	H	Me	2HCl	C ₁₈ H ₂₁ N ₃ O ₃ S.2HCl
275242	H	2-F-PhCH2NHCH2	H	Me	2HCl	C ₁₇ H ₁₈ FN ₃ O.2HCl

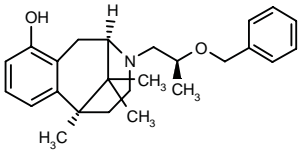
SOURCE – Schering AG.

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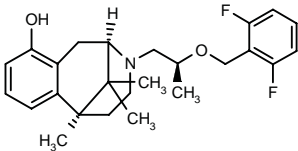
275626

(2*R*,6*S*)-3-[2(*S*)-Benzyloxypropyl]-6,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ol



C25 H33 N O2; Mol wt: 379.5407

ACTION – Voltage-dependent sodium channel blocker with potential in the treatment of cerebral ischemia, neurodegenerative disorders, hypoglycemia, hypoxia, anoxia, brain trauma, cerebral edema, stroke, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, myocardial infarction and angina pectoris. Another specifically claimed compound from this series of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ols is:



275627: C25 H31 F2 N O2

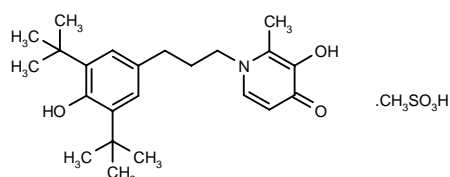
SOURCE – Boehringer Ingelheim.

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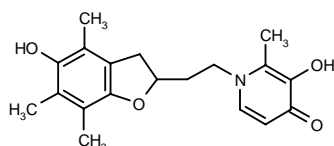
276705

1-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-3-hydroxy-2-methylpyridin-4(1*H*)-one methanesulfonate



C23 H33 N O3 . C H4 O3 S; Mol wt: 467.6233

ACTION – Neuroprotective agent with iron-chelating and antioxidant properties and potential in the treatment of conditions involving oxidative stress, particularly stroke. Antioxidant activity was demonstrated *in vitro* by inhibition of ascorbic acid-induced lipid peroxidation in rat brain homogenates ($IC_{50} = 0.4 \mu M$). In addition, compound was shown to protect cerebellar granule cells from iodoacetate-induced toxicity ($EC_{50} = 0.3 \mu M$). Its ability to inhibit oxidative stress was also assessed *in vitro* by inhibition of the iodoacetate-stimulated oxidation of dichlorohydrofluorescein (DCFH) to dichlorofluorescein (DCF) ($EC_{50} = 0.28 \mu M$). Compound was also effective in a rat model of oxidative stress induced by malonic acid and is reported to rapidly penetrate the brain. Another specifically claimed compound from this series of *ortho*-hydroxypyridinone derivatives is:



276707: C19 H23 N O4

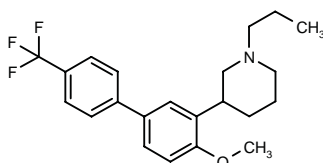
SOURCE – Cerebrus.

REFERENCES

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276708

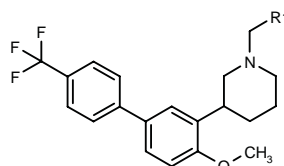
(+)-3-[4-Methoxy-4'-(trifluoromethyl)biphenyl-3-yl]-1-propylpiperidine



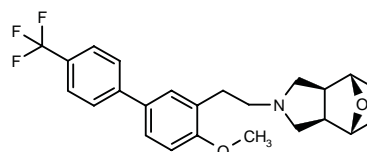
C22 H26 F3 N O; Mol wt: 377.4474

ACTION – Neuroprotective agent for the treatment of epilepsy, stroke, brain or spinal trauma and neurodegenerative disorders with affinity for veratridine-sensitive sodium channels and reported to block veratridine-induced glutamate release from rat hippocampal slices, provide long-lasting protection

against maximal electroshock-induced convulsions in mice and reduce ischemia-induced neuronal damage in the middle cerebral artery occlusion model in rats. Other specifically claimed compounds within this series of biphenyl derivatives include the following:



Compound	R1	Isomer	Formula
276710	Et	(-)	C ₂₂ H ₂₆ F ₃ NO
276711	H	(-)	C ₂₀ H ₂₂ F ₃ NO
276712	H	(+)	C ₂₀ H ₂₂ F ₃ NO



276713: C24 H26 F3 N O2

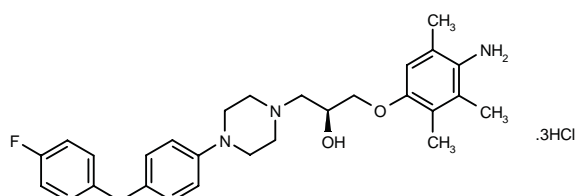
SOURCE – Novartis.

REFERENCES

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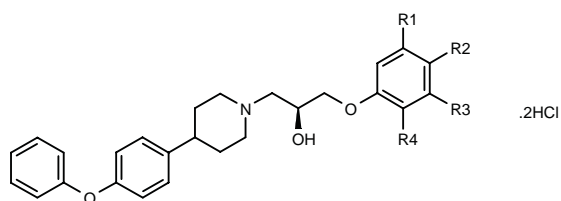
276717

1-(4-Amino-2,3,5-trimethylphenoxy)-3-[4-[4-(4-fluorobenzyl)phenyl]piperazin-1-yl]propan-2(*S*)-ol trihydrochloride

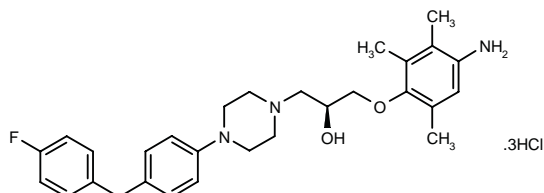


C29 H36 F N3 O2 . 3HCl; Mol wt: 587.0031

ACTION – Agent for the treatment or prevention of ischemic disorders, neurodegenerative diseases, epilepsy, migraine, diabetes, arteriosclerosis and inflammation that blocks T-type calcium and sodium channels and inhibits lipid peroxidation. Compound produced 27.9% inhibition of veratridine-induced activation of sodium channels in rat cerebral cortex at 0.1 μM , and it inhibited T-type Ca^{2+} channels in rat hippocampal CA1 cells with an IC_{50} of 3.0 μM . In addition, it inhibited lipid peroxidation in rat brain homogenates with an IC_{50} of 0.22 μM . *In vivo*, it produced 76% inhibition of audiogenic seizures in mice at 10 mg/kg i.p. $LD_{50} = 47.3$ mg/kg i.v. in mice. Within this series of arylpiperidino- and arylpiperazino-propanol derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
276719	Me	NH ₂	Me	Me	C ₂₉ H ₃₆ N ₂ O ₃ ·2HCl
276721	NH ₂	H	H	OMe	C ₂₇ H ₃₂ N ₂ O ₄ ·2HCl



276720: C₂₉ H₃₆ F N₃ O₂ · 3HCl

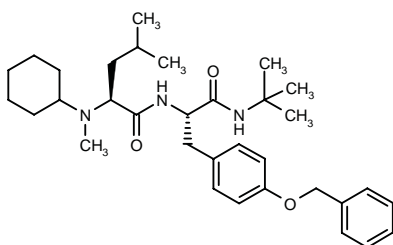
SOURCE – Suntory.

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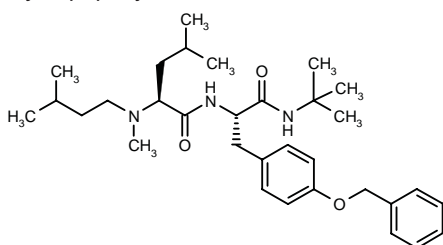
276863

N-Cyclohexyl-*N*-methyl-L-leucyl-4-*O*-(benzyl)-L-tyrosine *tert*-butylamide



C₃₃ H₄₉ N₃ O₃; Mol wt: 535.7681

ACTION – N-type calcium channel blocker, an analogue of PD-151307⁺ with an IC₅₀ value of 0.20 μM for blockade of calcium flux through N-type calcium channels in human neuroblastoma IMR-32 cells. Compound was able to block both neuronal N-type Ca²⁺ channel activity in superior cervical ganglion neurons and voltage-gated sodium channels (54% at 10 μM). *In vivo* in the audiogenic seizure model in mice, it was highly effective in preventing tonic seizures (100% protection at 10 mg/kg i.v.). Potentially useful for the treatment of stroke and chronic intractable pain. Another related compound in this class of *N,N*-dialkyl-dipeptidylamines is:



PD-175069 [274865]: C₃₂ H₄₉ N₃ O₃

SOURCES – Elan; Warner-Lambert.

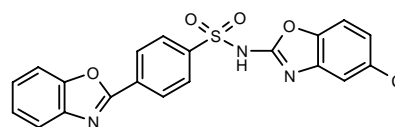
REFERENCES

1. Hu, L.-Y. et al. (Warner-Lambert Co.;Neurex Corp.) *Substd. peptidylamine calcium channel blockers.* WO 9854123.
2. Hu, L.-Y. et al. *N,N-Dialkyl-dipeptidylamines as novel N-type calcium channel blockers.* Bioorg Med Chem Lett 1999, 9(6): 907.
3. Ryder, T.R. et al. *PD 151307 analogs: Multiple parallel synthesis and biological evaluation of N,N-dialkylpeptidylamine derivatives as N-type calcium channel blockers.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 121.

⁺Drug Data Rep 1999, 021(05): 0403.

277362

4-(2-Benzoxazolyl)-*N*-(5-chlorobenzoxazol-2-yl)-benzenesulfonamide



C₂₀ H₁₂ Cl N₃ O₄ S; Mol wt: 425.8508

ACTION – Agent for the treatment of neurodegenerative disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia, amyotrophic lateral sclerosis, cerebral ischemia, epilepsy and spinal and head trauma that acts as a kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor. A representative compound within a series of benzenesulfonamide derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

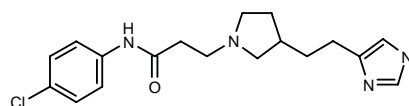
1. Varasi, M. et al. (Pharmacia & Upjohn SpA) *Benzenesulfonamide cpds.* WO 9928306.

RESPIRATORY DRUGS

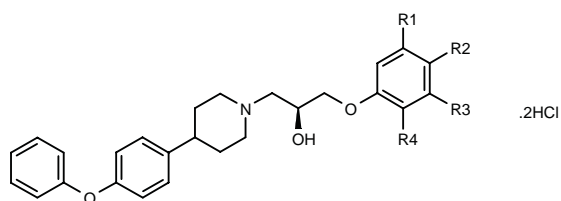
TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

276782

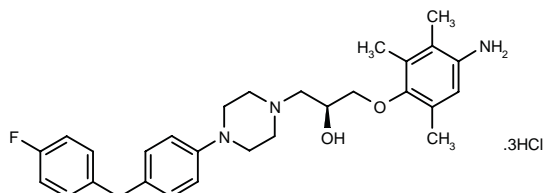
N-(4-Chlorophenyl)-3-[3-[2-(1*H*-imidazol-4-yl)ethyl]-1-pyrrolidinyl]propionamide



C₁₈ H₂₃ Cl N₄ O; Mol wt: 346.8597



Compound	R1	R2	R3	R4	Formula
276719	Me	NH ₂	Me	Me	C ₂₉ H ₃₆ N ₂ O ₃ ·2HCl
276721	NH ₂	H	H	OMe	C ₂₇ H ₃₂ N ₂ O ₄ ·2HCl



276720: C₂₉ H₃₆ F N₃ O₂ · 3HCl

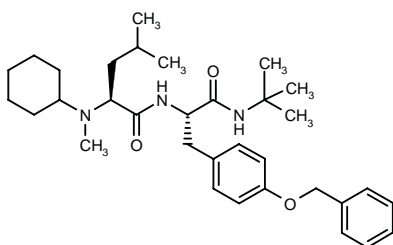
SOURCE – Suntory.

REFERENCES

1. Annoura, H. et al. (Suntory Ltd.) *Arylpiperidinopropanol and arylpiperazinopropanol derivs. and pharmaceuticals containing the same.* WO 9923072.

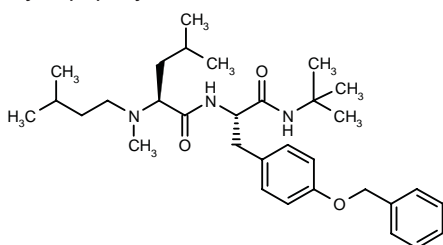
276863

N-Cyclohexyl-*N*-methyl-L-leucyl-4-*O*-(benzyl)-L-tyrosine *tert*-butylamide



C₃₃ H₄₉ N₃ O₃; Mol wt: 535.7681

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PD-175069 [274865]: C₃₂ H₄₉ N₃ O₃

SOURCES – Elan; Warner-Lambert.

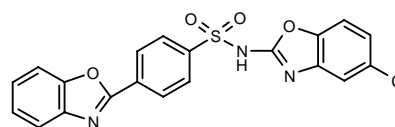
REFERENCES

1. Hu, L.-Y. et al. (Warner-Lambert Co.;Neurex Corp.) *Substd. peptidylamine calcium channel blockers.* WO 9854123.
2. Hu, L.-Y. et al. *N,N-Dialkyl-dipeptidylamines as novel N-type calcium channel blockers.* Bioorg Med Chem Lett 1999, 9(6): 907.
3. Ryder, T.R. et al. *PD 151307 analogs: Multiple parallel synthesis and biological evaluation of N,N-dialkylpeptidylamine derivatives as N-type calcium channel blockers.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI 121.

⁺Drug Data Rep 1999, 021(05): 0403.

277362

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ACTION – Agent for the treatment of neurodegenerative disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia, amyotrophic lateral sclerosis, cerebral ischemia, epilepsy and spinal and head trauma that acts as a kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor. A representative compound within a series of benzenesulfonamide derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

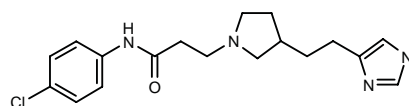
1. Varasi, M. et al. (Pharmacia & Upjohn SpA) *Benzenesulfonamide cpds.* WO 9928306.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

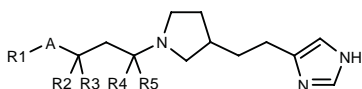
276782

N-(4-Chlorophenyl)-3-[3-[2-(1*H*-imidazol-4-yl)ethyl]-1-pyrrolidinyl]propionamide

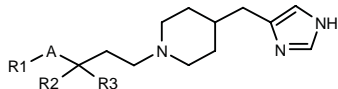


C₁₈ H₂₃ Cl N₄ O; Mol wt: 346.8597

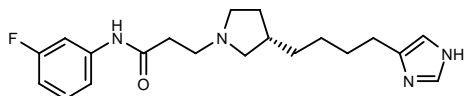
ACTION – Histamine H₃ receptor antagonist with high affinity for the receptor in binding assays, with K_i values in the range of 0.1-20 nM. Preferably for oral administration in the treatment of upper airways allergic responses, especially in combination with an H₁ antagonist such as loratadine or descarboethoxyloratadine. In addition, it may also be useful for the treatment of inflammation, cardiovascular diseases, hypotension, glaucoma, sleep disorders, disorders of the gastrointestinal tract and CNS, Alzheimer's disease, schizophrenia, obesity and migraine. Other specifically claimed heterocyclic-substituted imidazoalkyl compounds include the following:



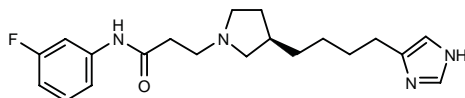
Compound	R1	R2	R3	R4	R5	A	Formula
276783	Ph	H	H	H	H	O	C ₁₈ H ₂₅ N ₃ O
276784	3,5-(Cl)2-Ph	-O-		H	H	NH	C ₁₈ H ₂₂ Cl ₂ N ₄ O
276785	Ph	H	H		-O-	O	C ₁₈ H ₂₃ N ₃ O ₂
276786	3-Cl-Ph	-O-		H	H	NH	C ₁₈ H ₂₃ ClN ₄ O
276787	3-F-Ph	-O-		H	H	NH	C ₁₈ H ₂₃ FN ₄ O
276788	4-Cl-PhCH ₂ CH ₂	-O-		H	H	NH	C ₂₀ H ₂₇ ClN ₄ O



Compound	R1	R2	R3	A1	Formula
276791	Ph	H	H	O	C ₁₈ H ₂₅ N ₃ O
276792	3-Cl-Ph	-O-		NH	C ₁₈ H ₂₃ ClN ₄ O
276793	4-Cl-PhCH ₂ CH ₂	-O-		NH	C ₂₀ H ₂₇ ClN ₄ O
276794	3,5-(Cl)2-Ph	-O-		NH	C ₁₈ H ₂₂ Cl ₂ N ₄ O
276795	4-Cl-Ph	-O-		NH	C ₁₈ H ₂₃ ClN ₄ O
276796	3-F-Ph	-O-		NH	C ₁₈ H ₂₃ FN ₄ O



276789: C₂₀ H₂₇ F N₄ O



276790: C₂₀ H₂₇ F N₄ O

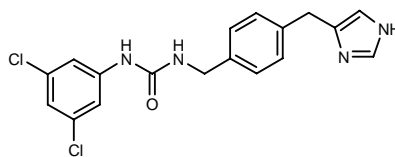
SOURCE – Schering-Plough.

REFERENCES

1. Vaccaro, W.D. et al. (Schering Corp.) Imidazoylalkyl subst. with a five, six or seven membered heterocyclic ring containing one nitrogen atom. WO 9924421.

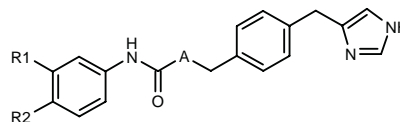
276824

N-(3,5-Dichlorophenyl)-*N'*-[4-(1*H*-imidazol-4-ylmethyl)-benzyl]urea



C₁₈ H₁₆ Cl₂ N₄ O; Mol wt: 375.2574

ACTION – Histamine H₃ receptor antagonist (K_i = 4-12 nM in guinea pig brain homogenates) with potential in the treatment of allergy, inflammation, cardiovascular disorders, glaucoma, sleep, gastrointestinal tract and CNS disorders, Alzheimer's disease, schizophrenia, obesity and migraine. In particular, methods of treating upper airways allergic responses in combination with an H₁ receptor antagonist such as loratadine or descarboethoxyloratadine are specifically claimed. Other specifically claimed compounds within this series of phenylalkyl imidazole derivatives include the following:



Compound	R1	R2	A	Formula
276825	Cl	Cl	NH	C ₁₈ H ₁₆ Cl ₂ N ₄ O
276826	H	OCF ₃	NH	C ₁₉ H ₁₇ F ₃ N ₄ O ₂
276827	CN	H	O	C ₁₉ H ₁₆ N ₄ O ₂
276828	Cl	H	O	C ₁₈ H ₁₆ ClN ₃ O ₂
276829	OMe	H	O	C ₁₉ H ₁₉ N ₃ O ₃
276830	H	H	CH ₂	C ₁₉ H ₁₉ N ₃ O
276831	Cl	H	CH ₂	C ₁₉ H ₁₈ ClN ₃ O

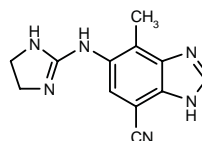
SOURCE – Schering-Plough.

REFERENCES

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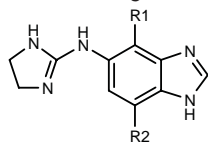
277105

5-(4,5-Dihydro-1*H*-imidazol-2-ylamino)-4-methyl-1*H*-benzimidazole-7-carbonitrile



C₁₂ H₁₂ N₆; Mol wt: 240.2688

ACTION – Selective, peripherally acting α_2 -adrenoceptor agonist with little or no effect on the CNS and reported to possess improved metabolic stability in primates compared to structurally related compounds. Potentially useful in the treatment or prevention of respiratory disorders, particularly nasal congestion, as well as ocular disorders, gastrointestinal disorders, migraine and peripheral pain. Other specifically claimed compounds from this series of 5-(2-imidazolinylamino)benzimidazole derivatives include the following:



Compound	R1	R2	Formula
277106	Me	OH	C ₁₁ H ₁₃ N ₅ O
277108	Et	Me	C ₁₃ H ₁₇ N ₅
277109	cyclopropyl	Me	C ₁₄ H ₁₇ N ₅

SOURCE – Procter & Gamble.

REFERENCES

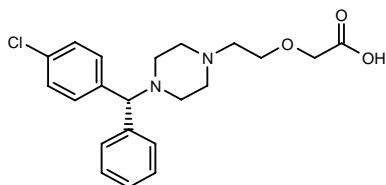
1. Cupps, T.L. et al. (The Procter & Gamble Co.) 5-(2-Imidazolinylamino)-benzimidazole derivs., their preparation and their use as α -adrenoceptor agonists with improved metabolic stability. WO 9926942.

LEVOCETIRIZINE

Prop INN

269103

(*R*)-2-[2-[4-[1-(4-Chlorophenyl)-1-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid



C21 H25 Cl N2 O3; Mol wt: 388.8925

ACTION – Histamine H₁ receptor antagonist, the optical (*R*)-enantiomer of racemic cetirizine (Zyrtec) currently in phase III clinical trials for the treatment of seasonal and perennial allergic rhinitis. Preclinical studies indicated that the single-isomer compound is a potent antihistamine potentially devoid of adverse effects including sedation and somnolence.

SOURCES – Sepracor; UCB.

REFERENCES

1. Cossement, E. et al. (UCB SA) Enantiomers of 1-[4-(chlorophenyl)phenylmethyl]-4-(methylphenyl)sulfonyl piperazine. EP 617028.
2. Cossement, E. et al. (UCB SA) Process for preparation of a 1-piperazine-ethoxyacetic acid. GB 2225321.
3. Gray, N.M. (Sepracor Inc.) Compsns. for treating allergic disorders using (-) cetirizine. EP 663828, JP 96501561, US 5698558, WO 9406429.
4. Gray, N.M. (Sepracor Inc.) Methods and compsns. for treating allergic disorders using optically pure (+) cetirizine. EP 661975, JP 96501562, WO 9406430.
5. Van De Venne, H. and Martin, J.-P. (UCB SA) Pharmaceutical compsns. for the treatment of rhinitis. GB 2311940.

6. Proposed international nonproprietary names (Prop. INN): List 78. WHO Drug Inf 1997, 11(4): 276.

7. Sepracor and UCB reach Zyrtec isomer licensing agreement. DailyDrugNews.com (Daily Essentials) 1999, June 3.

ASTHMA THERAPY

275392

D-Cysteiny-D-glutaminy-D-isoleucyl-D-tryptophyl-D-lysyl-D-glutaminy-D-lysyl-D-prolyl-D-aspartyl-D-leucyl-D-cysteine cyclic disulfide

C60 H94 N16 O16 S2; Mol wt: 1359.6310

ACTION – Chemokine modulator, a cyclic reverse-D peptide derivative of monocyte chemoattractant protein-1 (MCP-1) with potential in the treatment of chemokine-mediated disorders such as multiple sclerosis, asthma, psoriasis, allergy, rheumatoid arthritis, organ transplant rejection, HIV infection and autoimmune diseases. *In vitro*, compound was found to strongly bind to chemokine receptors on THP-1 cells and to inhibit MCP-1-induced migration of THP-1 cells with an IC₅₀ value of about 1 nM; in addition, compound is reported to inhibit THP-1 cell migration induced by other chemokines such as MIP-1 α , IL-8 and SDF1 with similar potency. Compound was also shown to inhibit the concanavalin-induced proliferation of CD4 T-cells by 50% at 50 ng. *In vivo*, it was effective in a rat skin inflammation model, where it markedly reduced MCP-1- and lipopolysaccharide (LPS)-induced recruitment of monocyte/macrophages following i.v. and s.c. administration. It was shown to be effective in a murine model of endotoxemia, producing a dose-dependent inhibition of LPS-induced tumor necrosis factor- α (TNF- α) production. When tested in a murine asthma model, compound decreased the percentage of CD3, CD4 and B220 cells in the lung following i.v. or i.t. administration. In addition, it reduced the cellular inflammation in the lung, IgE responses and serum IL-4 levels in ovalbumin-challenged mice when given i.v. and s.c. Another specifically claimed compound from this series of chemokine peptides, variants and derivatives is:

L-Cysteiny-L-leucyl-L-aspartyl-L-prolyl-L-lysyl-L-glutaminy-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamine

275393: C57 H91 N15 O15 S

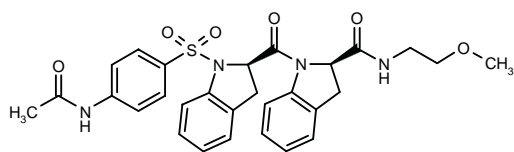
SOURCE – NeoRx.

REFERENCES

1. Grainger, D.J. et al. (NeoRx Corp.) Chemokine peptides, variants, derivs. and analogs. Their use in methods to inhibit or augment an inflammatory response. WO 9912968.

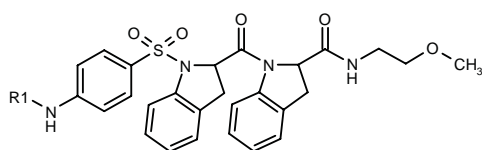
275678

1-[1-[4-(Acetamido)phenylsulfonyl]-2,3-dihydro-1*H*-indol-2(*R*)-ylcarbonyl]-*N*-(2-methoxyethyl)-2,3-dihydro-1*H*-indole-2(*R*)-carboxamide

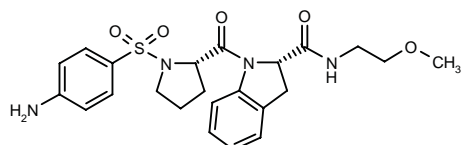


C₂₉H₃₀N₄O₆S; Mol wt: 562.6440

ACTION – Antiasthmatic, antiallergic, antiinflammatory and immunosuppressive agent with high affinity for immunophilins such as CypA, CypB, CypC and FKBP12, as demonstrated in binding assays. *In vitro*, compound was shown to inhibit the CD3-induced proliferation of T-cells (85% inhibition at 10 μmol). Other exemplified compounds include the following:



Compound	R1	Isomer	Formula
275679	Ac	(S,S)	C ₂₉ H ₃₀ N ₄ O ₆ S
275680	Ac	(S,R)	C ₂₉ H ₃₀ N ₄ O ₆ S
275681	Ac	(R,S)	C ₂₉ H ₃₀ N ₄ O ₆ S
275682	Ac	(RS,RS)	C ₂₉ H ₃₀ N ₄ O ₆ S
275683	H	(S,S)	C ₂₇ H ₂₈ N ₄ O ₆ S



275684: C₂₃H₂₈N₄O₅S

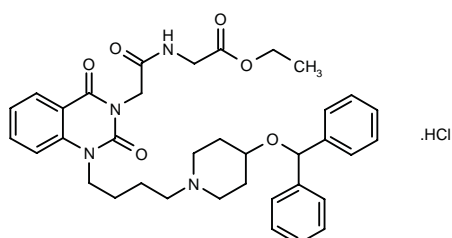
SOURCE – Asta Medica.

REFERENCES

1. Reichert, D. et al. (Asta Medica AG) *Specific immunophilin ligands useful as anti-asthmatic, anti-allergic, anti-rheumatic, immunosuppressive, antipsoriatic and neuroprotective agents*. WO 9915501.

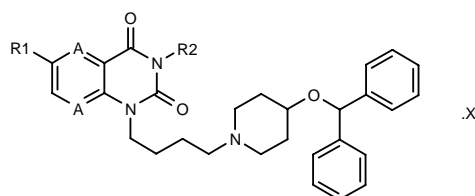
276258

2-[2-[1-[4-[4-(Diphenylmethoxy)piperidin-1-yl]butyl]-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3(2*H*)-yl]-*N*-methylacetamido]acetic acid ethyl ester hydrochloride



C₃₇H₄₄N₄O₆ · HCl; Mol wt: 677.2375

ACTION – Agent for the treatment of asthma, allergic conjunctivitis, allergic rhinitis, urticaria and atopic dermatitis with antihistaminic and eosinophil chemotaxis-inhibitory activity. *In vitro*, compound produced 122% inhibition of LTB₄-induced guinea pig eosinophil chemotaxis at 10 μM. Other exemplified compounds from this series of nitrogen-containing fused-ring derivatives include the following:



Compound	R1	R2	A	X	Formula
276259	H	H	CH		C ₃₀ H ₃₃ N ₃ O ₃
276260	H	H	N		C ₂₈ H ₃₁ N ₅ O ₃
276262	NH ₂	H	CH		C ₃₀ H ₃₄ N ₄ O ₃
276263	H	CH ₂ CO ₂ CH ₂ CO ₂ Me	CH	HCl	C ₃₅ H ₃₉ N ₃ O ₇ ·HCl

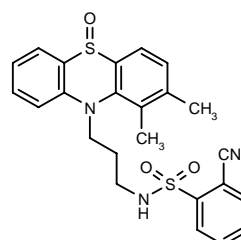
SOURCE – Takeda.

REFERENCES

1. Kajino, M. et al. (Takeda Chemical Industries, Ltd.) *Nitrogenous fused-ring cpds., process for the preparation of the same, and drugs*. JP 99152275, WO 9914203.

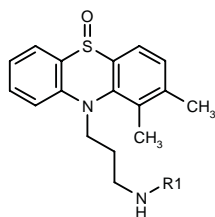
276585

2-Cyano-*N*-[3-(1,2-dimethyl-5-oxidophenothiazin-10-yl)-propyl]benzenesulfonamide



C₂₄H₂₃N₃O₃S₂; Mol wt: 465.5957

ACTION – Antiasthmatic and antiallergic agent that acts by inhibiting the release of chemical mediators such as 5-HT. Compound inhibited 5-HT release from rat RBL-2H3 cells with an IC₅₀ value of 2 μM. In addition, compound was found to inhibit 72-kDa tyrosine kinase activation caused by antigen stimulation in RBL-2H3 cells (100% inhibition at 10 μM). Within this series of phenothiazine compounds, the following are also included:



Compound	R1	Formula
276586	SO ₂ Ph	C ₂₃ H ₂₄ N ₂ O ₃ S ₂
276587	2-Cl-PhSO ₂	C ₂₃ H ₂₃ ClN ₂ O ₃ S ₂
276588	4-F-PhSO ₂	C ₂₃ H ₂₃ FN ₂ O ₃ S ₂
276589	COPh	C ₂₄ H ₂₄ N ₂ O ₂ S

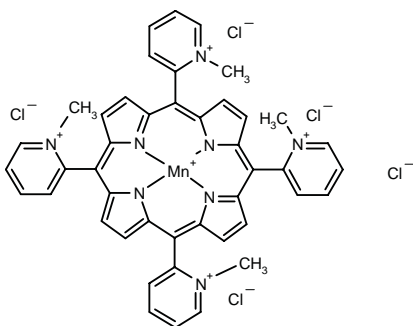
SOURCE – Eisai.

REFERENCES

1. Miyamoto, M. et al. (Eisai Co., Ltd.) *Novel phenothiazine derivs. and their medicines*. JP 99100373.

276723

[5,10,15,20-Tetrakis(1-methylpyridinium-2-yl)porphyrin]-manganese(III) pentachloride



C44 H36 Cl5 Mn N8; Mol wt: 909.0274

ACTION – Manganese complex of a low-molecular-weight porphyrin useful as an antioxidant, proven to potently inhibit iron/ascorbate-mediated lipid peroxidation (IC₅₀ = 1.0 μM) and to significantly reduce antigen-induced airways hyperreactivity in sensitized mice when given by intratracheal instillation daily for 4 days at a dose of 2 μg. The use of this complex in the treatment of asthma is specifically claimed, although it may find application in a wide range of disorders involving reactive oxygen species.

SOURCE – Duke University, Durham, NC (US).

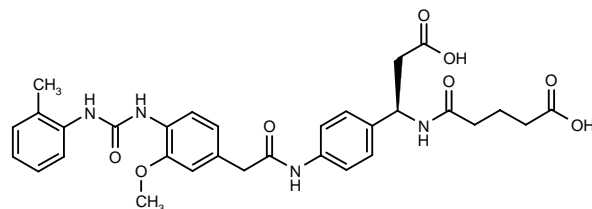
REFERENCES

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276736

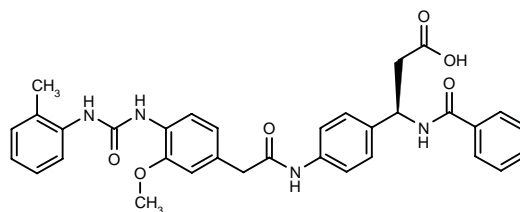
5-[2-Carboxy-1 (*R*)-[4-[2-[3-methoxy-4-[*N*³-(2-methylphenyl)ureido]phenyl]acetamido]phenyl]ethylamino]-5-oxopentanoic acid

N-[2-Carboxy-1 (*R*)-[4-[2-[3-methoxy-4-[*N*'-(2-methylphenyl)ureido]phenyl]acetamido]phenyl]ethyl]glutaramic acid



C31 H34 N4 O8; Mol wt: 590.6296

ACTION – Antiasthmatic and antiinflammatory agent that blocks the interaction of vascular cell adhesion molecule-1 (VCAM-1) and fibronectin with the integrin VLA-4 (α₄β₁) receptor. Another specifically claimed compound from this series of substituted anilide derivatives is:



276737: C33 H32 N4 O6

SOURCE – Rhône-Poulenc Rorer.

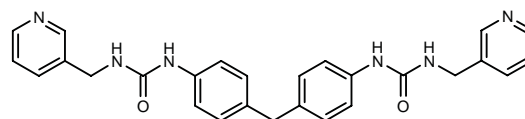
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276774

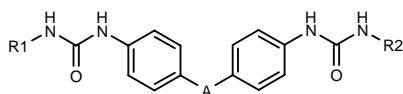
N'-(3-Pyridinylmethyl)-*N*-[4-[4-[*N*'-(3-pyridinylmethyl)ureido]benzyl]phenyl]urea

Bis[4-[3-(3-pyridylmethyl)ureido]phenyl]methane



C27 H26 N6 O2; Mol wt: 466.5424

ACTION – Agent for the treatment of allergy, asthma, atopic diseases, transplant rejection, cancer, parasitic diseases, leprosy, fungal infections, HIV infection, inflammation and scleroderma with IL-4- and IL-13-inhibitory activity. Within this series of *N,N'*-substituted urea derivatives, the following are also specifically claimed:



Compound	R1=R2	A	Formula
276775	3-Pyr-CH ₂	-O-	C ₂₆ H ₂₄ N ₆ O ₃
276776	2-pyrazinyl	-CH ₂ -	C ₂₃ H ₂₀ N ₆ O ₂
276777	3-Pyr-CH ₂	-(CH ₂) ₂ -	C ₂₈ H ₂₈ N ₆ O ₂
276778	3-Pyr-CH ₂	-CO-	C ₂₇ H ₂₄ N ₆ O ₃

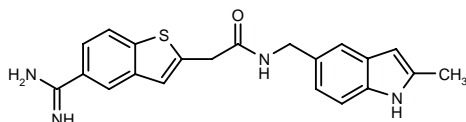
SOURCE – Schering AG.

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1. Buchmann, B. et al. (Schering AG) *N,N'*-Subst. carbamides used as a medicament. WO 9924403.

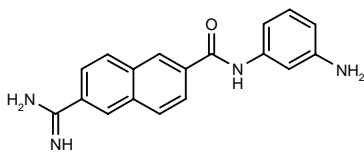
276821

2-(5-Amidino-1-benzothien-2-yl)-N-(2-methyl-1H-indol-5-ylmethyl)acetamide

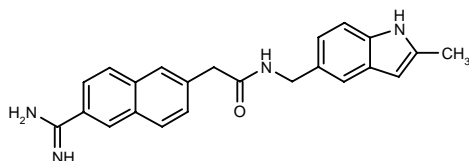


C₂₁ H₂₀ N₄ O S; Mol wt: 376.4820

ACTION – Agent for the treatment or prophylaxis of inflammatory diseases, particularly those mediated by mast cell activation, a potent inhibitor of human lung tryptase ($K_i = 0.041 \mu\text{M}$) with selectivity relative to other proteases such as trypsin ($K_i = 2.4 \mu\text{M}$), thrombin ($K_i = 25.8 \mu\text{M}$), factor Xa ($K_i = 17.7 \mu\text{M}$), plasmin ($K_i = 2.7 \mu\text{M}$), plasma kallikrein ($K_i = 1.6 \mu\text{M}$) and tissue kallikrein ($K_i > 100 \mu\text{M}$). Claimed for the treatment of asthma, allergic rhinitis, rheumatoid arthritis, dermatological diseases, multiple sclerosis, conjunctivitis, inflammatory bowel disease, anaphylaxis, osteoarthritis, peptic ulcer or cardiovascular diseases. Other representative compounds are:



276822: C₁₈ H₁₆ N₄ O



276823: C₂₃ H₂₂ N₄ O

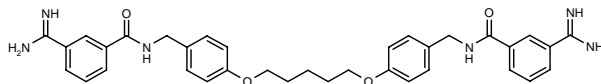
SOURCE – Amgen.

REFERENCES

1. Burgess, L. and Rizzi, J.P. (Amgen Inc.) *Cpds. which inhibit tryptase activity*. WO 9924407.

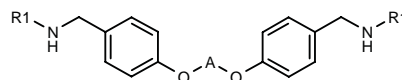
276927^{1,2}

N,N'-Pentane-1,5-dioldioxy-bis(1,4-phenylene)bismethylenebis(3-aminobenzamide)



C₃₅ H₃₈ N₆ O₄; Mol wt: 606.7232

ACTION – Agent for the treatment of inflammatory disorders of the respiratory tract such as asthma and allergic rhinitis, as well as other types of inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, conjunctivitis, psoriasis, scleroderma and inflammatory bowel disease, a potent inhibitor of the human mast cell protease tryptase ($K_i = 0.01 \mu\text{M}$) with selectivity relative to other proteases such as trypsin ($K_i = 0.9 \mu\text{M}$), thrombin ($K_i > 100 \mu\text{M}$), factor Xa ($K_i = 1.8 \mu\text{M}$), plasmin ($K_i = 7.6 \mu\text{M}$), elastase ($K_i > 100 \mu\text{M}$), plasma kallikrein ($K_i = 11.0 \mu\text{M}$), tissue kallikrein ($K_i > 100 \mu\text{M}$), cathepsin G ($K_i > 100 \mu\text{M}$) and chymotrypsin ($K_i > 100 \mu\text{M}$). *In vivo*, compound inhibited antigen-induced airways hyper-responsiveness in guinea pigs (107% inhibition at 1 mg/kg i.t.). Other exemplified compounds include the following:



Compound	R1	A	Formula
276928 ^{1,2}	3-[NH ₂ C(=NH)]-PhSO ₂	-(CH ₂) ₅ -	C ₃₃ H ₃₈ N ₆ O ₆ S ₂
276930 ^{1,2}	3-[NH ₂ C(=NH)]-PhSO ₂	-(CH ₂) ₄ -	C ₃₂ H ₃₆ N ₆ O ₆ S ₂
276931 ^{1,2}	4-[NH ₂ C(=NH)]-PhSO ₂	-(CH ₂) ₃ -	C ₃₁ H ₃₄ N ₆ O ₆ S ₂
276933 ^{1,2}	4-[NH ₂ C(=NH)]-PhCO	-(CH ₂) ₅ -	C ₃₅ H ₃₈ N ₆ O ₄
276934 ^{1,2}	4-[NH ₂ C(=NH)]-PhCO	-(CH ₂) ₆ -	C ₃₆ H ₄₀ N ₆ O ₄
276935 ¹	5-[NH ₂ C(=NH)]-2-benzimidazolyl-CH ₂ CO	-(CH ₂) ₅ -	C ₃₉ H ₄₂ N ₁₀ O ₄

SOURCE – Array BioPharma.

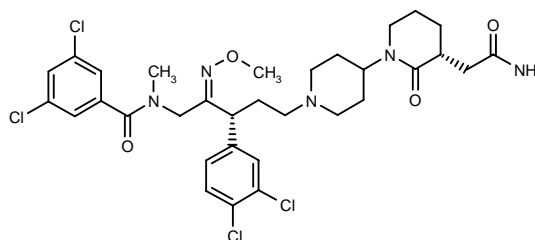
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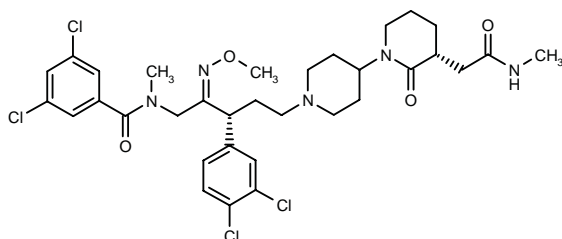
277118

N-[5-[4-[3(*R*)-(Carbamoylmethyl)-2-oxopiperidin-1-yl]-piperidin-1-yl]-3(*R*)-(3,4-dichlorophenyl)-2-(methoxyimino)pentyl]-*N*-methyl-3,5-dichlorobenzamide



C₃₂ H₃₉ Cl₄ N₅ O₄; Mol wt: 699.5031

ACTION – Agent for the treatment of asthma, cough, chronic obstructive pulmonary disease, bronchospasm, inflammatory disorders such as arthritis, emesis, neurodegenerative diseases, CNS disorders such as migraine and epilepsy, gastrointestinal disorders such as Crohn's disease and pain that acts by virtue of its tachykinin receptor-antagonist activity. Another specifically claimed compound from this series of substituted oximes is:



277119: C₃₃ H₄₁ Cl₄ N₅ O₄

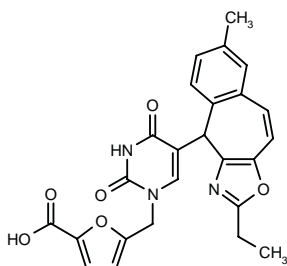
SOURCE – Schering-Plough.

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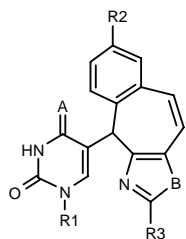
277156

(±)-5-[5-(2-Ethyl-7-methyl-4*H*-benzo[5,6]cyclohepta-[1,2-*d*]oxazol-4-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]furan-2-carboxylic acid

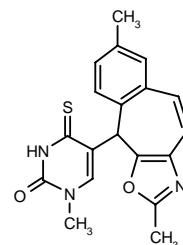


C₂₅ H₂₁ N₃ O₆; Mol wt: 459.4559

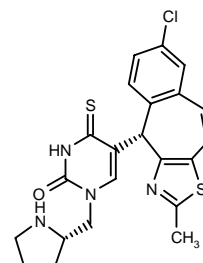
ACTION – Antiinflammatory agent, a P2Y₂ receptor antagonist. Within this series of specifically claimed pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	A	B	Formula
277157	3-[5-CF ₃ -1,2,4-triazol-3-yl-NHCO]-PhCH ₂	Et	Me	S	O	C ₃₀ H ₂₄ F ₃ N ₇ O ₃ S
277159	1-pyrrolidinyl-CH ₂ CH ₂	Me	Me	S	S	C ₂₄ H ₂₈ N ₄ O ₂ S ₂
277164	Me	Cl	N(Me) ₂	O	S	C ₁₉ H ₁₇ ClN ₄ O ₂ S
277165	CH ₂ CH ₂ OH	Cl	Me	S	S	C ₁₉ H ₁₆ ClN ₃ O ₂ S ₂
277166	Me	Cl	2-imid-azoyl-S	S	S	C ₂₀ H ₁₄ ClN ₅ O ₃



277158: C₁₉ H₁₇ N₃ O₂ S



277163: C₂₂ H₂₁ Cl N₄ O S₂

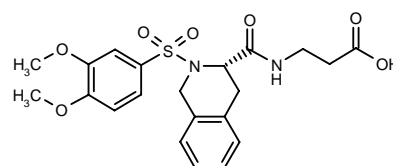
SOURCE – AstraZeneca.

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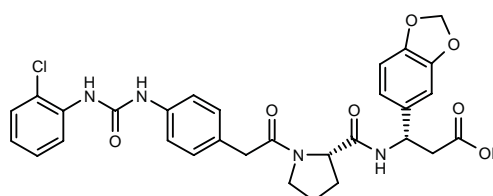
277191

N-[2-(3,4-Dimethoxyphenylsulfonyl)-1,2,3,4-tetrahydro-isoquinolin-3(*S*)-ylcarbonyl]-β-alanine

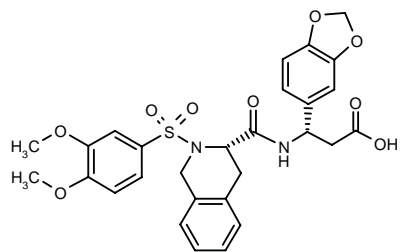


C₂₁ H₂₄ N₂ O₇ S; Mol wt: 448.4936

ACTION – Cell adhesion inhibitor that acts as an antagonist of VLA-4 (very late antigen-4, CD49d/CD29 or α₄β₁) and/or α₄β₇ (LPAM-1 or α₄β_p) integrins and thereby blocks the binding of VLA-4 and/or α₄β₇ to their ligands, including VCAM-1 and fibronectin. Potentially useful in the treatment or prevention of disorders such as multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease, psoriasis, tumor metastasis and atherosclerosis. Other exemplified substituted β-alanine derivatives include the following:



277192: C₃₀ H₂₉ Cl N₄ O₇



277193: C28 H28 N2 O9 S

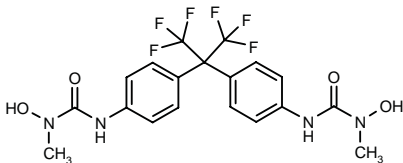
SOURCE – Merck & Co.

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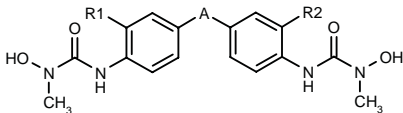
277344

4,4´-(Hexafluoroisopropylidene)bis(*N*-hydroxy-*N*-methyl-*N*′-phenylurea)



C19 H18 F6 N4 O4; Mol wt: 480.3632

ACTION – Antiallergic, antiasthmatic and antiinflammatory agent, a 5-lipoxygenase inhibitor (IC₅₀ = 0.024 μM in human leukocytes) found to inhibit LTB₄ production in human whole blood (IC₅₀ = 0.7 μM) and LTC₄ production in murine peritoneal macrophages (91% inhibition at 0.1 μM). Other compounds from this series of bishydroxyureas include the following:



Compound	R1	R2	A	Formula
277345	H	H	-O-	C ₁₆ H ₁₈ N ₄ O ₅
277346	OMe	OMe	bond	C ₁₈ H ₂₂ N ₄ O ₆

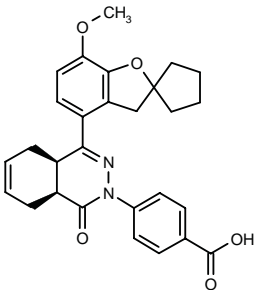
SOURCE – Minnesota Mining & Manufacturing (3M).

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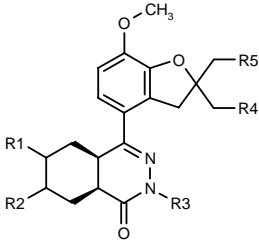
278121

cis-4-[4-(7-Methoxyspiro[2,3-dihydro-1-benzofuran-2,1′-cyclopentan]-4-yl)-1-oxo-1,2,4a,5,8,8a-hexahydro-phthalazin-1-yl]benzoic acid



C28 H28 N2 O5; Mol wt: 472.5382

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4; –logIC₅₀ = 9.38) and therefore suitable especially for the treatment of airways disorders and dermatoses, and also for erectile dysfunction. Other exemplified dihydrobenzofurans are:



Compound	R1	R2	R3	R4	R5	Formula
278122	bond		cyclopentyl	-(CH2)2-		C ₂₆ H ₃₂ N ₂ O ₃
278123	bond		cycloheptyl	-(CH2)2-		C ₂₈ H ₃₆ N ₂ O ₃
278124	H	H	cycloheptyl	-(CH2)2-		C ₂₈ H ₃₈ N ₂ O ₃
278125	bond		cycloheptyl	H	H	C ₂₆ H ₃₄ N ₂ O ₃

SOURCE – Byk Gulden.

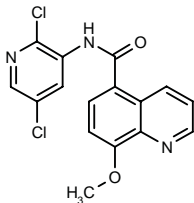
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D-4418

241381

N-(2,5-Dichloro-3-pyridinyl)-8-methoxyquinoline-5-carboxamide



C16 H11 Cl2 N3 O2; Mol wt: 348.1879

ACTION – Potent and selective human phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 200 nM) that is devoid of activity against other human PDEs, as well as against a range of other enzymes and receptors. Compound increased intracellular cAMP in leukocytes and inhibited the lipopolysaccharide (LPS)-induced release of tumor necrosis factor (TNF; IC_{50} = 160 nM) and the mitogen-induced release of IL-5 (IC_{50} = 500 nM) in human peripheral blood mononuclear cells. *In vivo*, it inhibited the LPS-induced increase in plasma TNF levels (ED_{50} = 10 mg/kg p.o.) in rats. In allergic guinea pigs it inhibited (10 mg/kg p.o.) antigen-induced eosinophil influx into bronchoalveolar lavage, as well as early- and late-phase bronchoconstriction (44 and 100% inhibition, respectively); it also completely blocked U-46619-induced bronchoconstriction at this dose. D-4418 showed good safety in both dogs (up to 60 mg/kg p.o.) and ferrets (up to 50 mg/kg p.o.). In phase I clinical trials it was well tolerated and showed good absorption. Potentially useful as an antiasthmatic, antiallergic and antiinflammatory agent.

SOURCES – Chiroscience; Schering-Plough.

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LEVALBUTEROL HYDROCHLORIDE

USAN

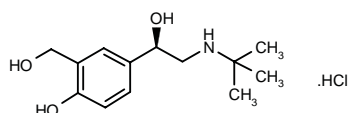
220684

(-)-(R)- α -(*tert*-Butylaminomethyl)-4-hydroxy-*m*-xylene- α,α' -diol hydrochloride

(-)-(R)- α^1 -(*tert*-Butylaminomethyl)-4-hydroxy-1,3-benzene-dimethanol hydrochloride

(R)-Albuterol hydrochloride

Levosalbutamol hydrochloride (Prop INN)



C₁₃ H₂₁ N O₃; Mol wt: 239.3129

ACTION – β_2 -Adrenoceptor agonist that relaxes airways smooth muscle irrespective of the spasmogen, the active (R)-enantiomer of the bronchodilator albuterol*.

INDICATION – Treatment or prevention of bronchospasm in adults and children 12 years of age and older with reversible obstructive airways disease.

PRESENTATION – Vials (3 ml), solution for inhalation, equivalent to 0.63 and 1.25 mg of levalbuterol.

PROPRIETARY NAME – Xopenex (US).

SOURCE – Sepracor.

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35. Sepracor Inc. Annual Report 1995.

36. Sepracor Inc. First Quarter Report 1995.

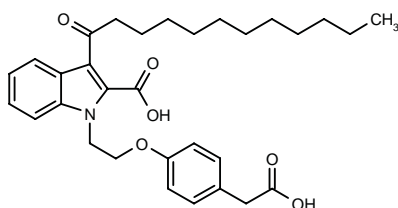
47. Sepracor Inc. Second Quarter Report 1995.

*See **Salbutamol** Drug Data Report 1988, 010(02): 0101.

ML-3176

277543

1-[2-[4-(Carboxymethyl)phenoxy]ethyl]-3-(1-dodecanoyl)-1*H*-indole-2-carboxylic acid



C31 H39 N O6; Mol wt: 521.6501

ACTION – Cytosolic phospholipase A₂ (cPLA₂) inhibitor (IC₅₀ = 1.6 μM in bovine platelets) able to reduce carrageenan-induced paw edema in rats by about 68% at 100 mg/kg i.p. and phorbol ester-induced ear irritation by 82% at 1 mg/ear topically. In allergic sheep, compound (100 mg by inhalation) protected against antigen-induced late airways response and completely prevented the airways hyperresponsiveness to inhaled carbachol.

SOURCE – Merckle.

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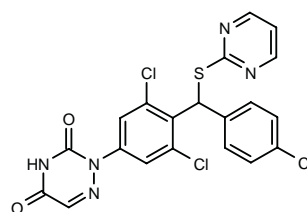
1. Lehr, M. (Merckle GmbH) *Acylpyrroldicarboxylic acids and acylindoldicarboxylic acids and their derivs. and inhibitors of the cytosolic phospholipase A2.* EP 923546, WO 9805637.

2. Tries, S. et al. *Effects of ML 3176, an inhibitor of cPLA2, on carrageenan-induced PAW edema, phorbol ester-induced mouse ear edema and in a sheep model of asthma.* Mediators Inflamm 1999, 8(Suppl. 1): Abst P-11-34.

R-146225*

272556

(-)-2-[3,5-Dichloro-4-[1-(4-chlorophenyl)-1-(2-pyrimidinylsulfanyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione



C20 H12 Cl3 N5 O2 S; Mol wt: 492.7728

ACTION – Potent, selective and orally active inhibitor of IL-5 biosynthesis as demonstrated in mitogen-stimulated human whole blood and murine splenocytes, where it inhibited the production of IL-5 with IC₅₀ values of 34 and 6 nM, respectively; it had no effect on IL-2, IL-4 or IL-13 production, whereas it did stimulate the production of interferon gamma and induced a selective downregulation of IL-5 mRNA expression. *In vivo* compound (0.04-2.5 mg/kg p.o.) decreased serum IL-5 protein and spleen IL-5 mRNA production induced by CD3 antibody or staphylococcal enterotoxin. Potentially useful for the treatment of allergic diseases.

SOURCE – Janssen.

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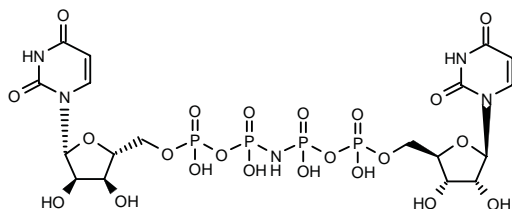
2. Van Wauwe, J. et al. *Identification of R146225 as a novel orally active inhibitor of interleukin-5 protein and mRNA production.* Mediators Inflamm 1999, 8(Suppl. 1): Abst S-05-4.

*Identified compound **272556** Drug Data Report 1999, 021(04): 0314.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

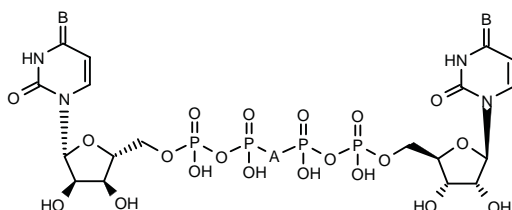
275753

*P*¹,*P*⁴-Di(uridine-5'-*P*²,*P*³-imidinotetraphosphate)

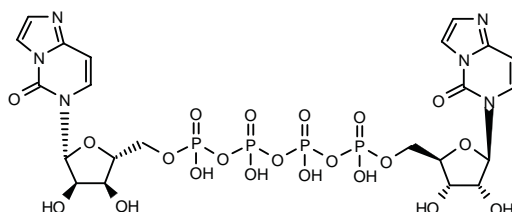


C18 H27 N5 O22 P4; Mol wt: 789.3203

ACTION – Agent for the treatment of chronic obstructive pulmonary diseases including chronic bronchitis, sinusitis, otitis media, pneumonia and cystic fibrosis, a selective agonist of the P2Y₂ receptor relative to the P2Y₁, P2Y₄ and P2Y₆ receptors, as measured in the inositol phosphate assay (EC₅₀ = 0.63, 3.67, 1.19 and 2.56 μM, respectively). Other specifically claimed dinucleotide derivatives include the following:



Compound	A	B	Formula
275754	-CH2-	O	C ₁₉ H ₂₈ N ₄ O ₂₂ P ₄
275755	-C(F)2-	O	C ₁₉ H ₂₆ F ₂ N ₄ O ₂₂ P ₄
275756	-O-	S	C ₁₈ H ₂₆ N ₄ O ₂₁ P ₄ S ₂
275757	-OPO(OH)O-	O	C ₁₈ H ₂₇ N ₄ O ₂₆ P ₅



275758: C22 H28 N6 O21 P4

SOURCE – Inspire Pharmaceuticals.

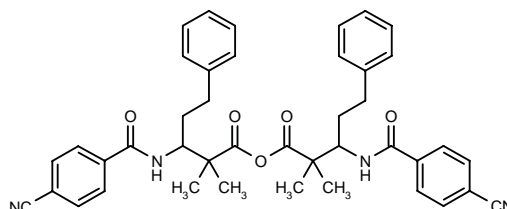
REFERENCES

1. Pendergast, W. et al. (Inspire Pharmaceuticals, Inc.) *Dinucleotides and their use as modulators of mucociliary clearance and ciliary beat frequency*. US 5837861.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

274608

3-(4-Cyanobenzamido)-2,2-dimethyl-5-phenylpentanoic acid anhydride



C42 H42 N4 O5; Mol wt: 682.8168

ACTION – Chymotrypsin-like serine protease inhibitor with IC₅₀ values of 1.0, 70 and 180 nM, respectively, for bovine chymotrypsin, human chymase and human cathepsin G, and high selectivity over other proteases such as rabbit angiotensin-converting enzyme (ACE; IC₅₀ > 100 μM). No mortality was observed following administration of 10 mg/kg/day p.o. x 2 weeks to rats.

SOURCE – Nippon Steel.

REFERENCES

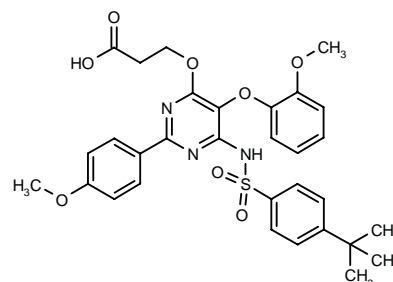
1. Ito, K. and Igarashi, K. (Nippon Steel Corp.) *Novel acid anhydrides, and chymotrypsin-like protease inhibitors*. JP 99049739.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

274612

3-[6-(4-*tert*-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2-(4-methoxyphenyl)-4-pyrimidinyl]propionic acid



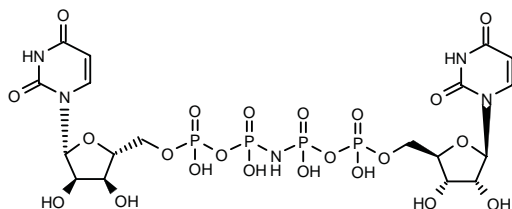
C31 H33 N3 O8 S; Mol wt: 607.6807

ACTION – Endothelin receptor antagonist with selectivity for ET_B receptors, as demonstrated in a binding assay by IC₅₀ values of 23.8 and 0.22 μM, respectively, for ET_A and ET_B receptors. Other compounds from this series of pyrimidine derivatives include the following:

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

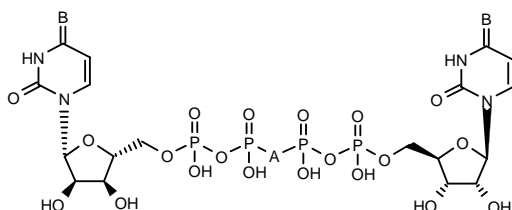
275753

*P*¹,*P*⁴-Di(uridine-5'-*P*²,*P*³-imidinotetraphosphate)

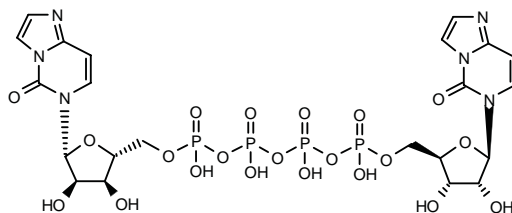


C18 H27 N5 O22 P4; Mol wt: 789.3203

ACTION – Agent for the treatment of chronic obstructive pulmonary diseases including chronic bronchitis, sinusitis, otitis media, pneumonia and cystic fibrosis, a selective agonist of the P2Y₂ receptor relative to the P2Y₁, P2Y₄ and P2Y₆ receptors, as measured in the inositol phosphate assay (EC₅₀ = 0.63, 3.67, 1.19 and 2.56 μM, respectively). Other specifically claimed dinucleotide derivatives include the following:



Compound	A	B	Formula
275754	-CH2-	O	C ₁₉ H ₂₈ N ₄ O ₂₂ P ₄
275755	-C(F)2-	O	C ₁₉ H ₂₆ F ₂ N ₄ O ₂₂ P ₄
275756	-O-	S	C ₁₈ H ₂₆ N ₄ O ₂₁ P ₄ S ₂
275757	-OPO(OH)O-	O	C ₁₈ H ₂₇ N ₄ O ₂₆ P ₅



275758: C22 H28 N6 O21 P4

SOURCE – Inspire Pharmaceuticals.

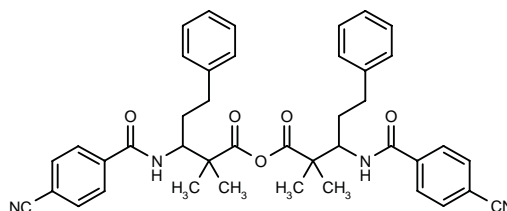
REFERENCES

1. Pendergast, W. et al. (Inspire Pharmaceuticals, Inc.) *Dinucleotides and their use as modulators of mucociliary clearance and ciliary beat frequency*. US 5837861.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

274608

3-(4-Cyanobenzamido)-2,2-dimethyl-5-phenylpentanoic acid anhydride



C42 H42 N4 O5; Mol wt: 682.8168

ACTION – Chymotrypsin-like serine protease inhibitor with IC₅₀ values of 1.0, 70 and 180 nM, respectively, for bovine chymotrypsin, human chymase and human cathepsin G, and high selectivity over other proteases such as rabbit angiotensin-converting enzyme (ACE; IC₅₀ > 100 μM). No mortality was observed following administration of 10 mg/kg/day p.o. x 2 weeks to rats.

SOURCE – Nippon Steel.

REFERENCES

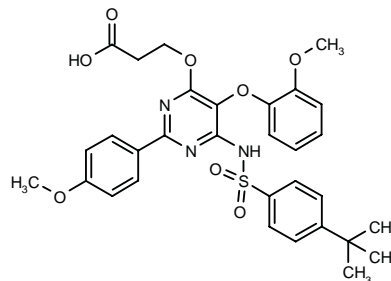
1. Ito, K. and Igarashi, K. (Nippon Steel Corp.) *Novel acid anhydrides, and chymotrypsin-like protease inhibitors*. JP 99049739.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

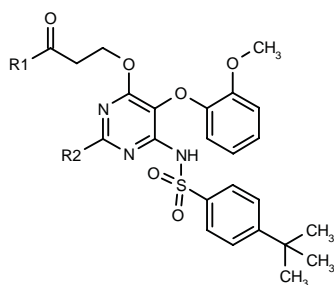
274612

3-[6-(4-*tert*-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2-(4-methoxyphenyl)-4-pyrimidinyl]propionic acid



C31 H33 N3 O8 S; Mol wt: 607.6807

ACTION – Endothelin receptor antagonist with selectivity for ET_B receptors, as demonstrated in a binding assay by IC₅₀ values of 23.8 and 0.22 μM, respectively, for ET_A and ET_B receptors. Other compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	Formula
274613	OMe	4-MeO-Ph	C ₃₂ H ₃₆ N ₃ O ₆ S
274614	OCH ₂ Ph	4-MeO-Ph	C ₃₈ H ₃₉ N ₃ O ₆ S
274616	2-Et-PhNH	4-MeO-Ph	C ₃₉ H ₄₂ N ₄ O ₇ S
274617	2,6-(Me)2-PhNH	4-MeO-Ph	C ₃₉ H ₄₂ N ₄ O ₇ S
274620	2-Pyr-NH	4-MeO-Ph	C ₃₆ H ₃₇ N ₅ O ₇ S
274621	OH	2-Pyr	C ₂₉ H ₃₀ N ₄ O ₇ S
274623	2-i-Pr-PhNH	2-Pyr	C ₃₈ H ₄₁ N ₅ O ₆ S
274628	2-Pyr-NH	3,5-(EtO)2-Ph	C ₃₉ H ₄₃ N ₅ O ₆ S

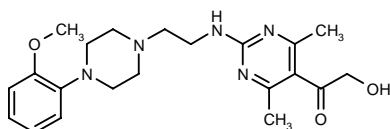
SOURCE – Kowa.

REFERENCES

- Hirata, M. et al. (Kowa Co., Ltd.) *Pyrimidine derivs.* JP 99043482.

276570

2-Hydroxy-1-[2-[2-[4-(2-methoxyphenyl)-1-piper-aziny]ethylamino]-4,6-dimethyl-5-pyrimidinyl]-1-ethanone



C₂₁ H₂₉ N₅ O₃; Mol wt: 399.4921

ACTION – Agent for the treatment of hypertension, cardiac, cerebral and peripheral ischemic disorders, heart failure, arrhythmia and dysuria, an α_1 -adrenoceptor antagonist with similar affinity for prostatic and vascular receptors ($IC_{50} = 0.0233$ and 0.0248 μ M, respectively, for inhibition of phenylephrine-induced contractions of canine prostate and carotid artery). Compound exhibited good oral absorption when administered to rats at 3 mg/kg p.o.

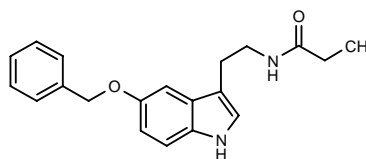
SOURCE – Ono.

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- Hashimoto, S. et al. (Ono Pharmaceutical Co., Ltd.) *Novel pyrimidine derivs.* JP 99092458.

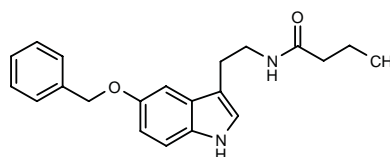
276732

N-[2-(5-Benzyloxyindol-3-yl)ethyl]propionamide



C₂₀ H₂₂ N₂ O₂; Mol wt: 322.4058

ACTION – Antihypertensive agent, a derivative of *N*-acetylserotonin (NAS) that was found to be more potent than NAS in lowering blood pressure in spontaneously hypertensive rats (SHR) when given at 30 mg/kg s.c. (24 and 12% decrease in blood pressure, respectively). Another compound from this series of *N*-acetylserotonin derivatives is:



276734: C₂₁ H₂₄ N₂ O₂

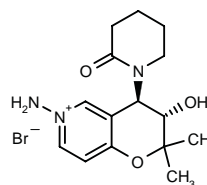
SOURCE – St. Elizabeth's Medical Center of Boston, Boston, MA (US).

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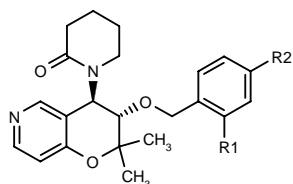
276806

trans-6-Amino-3-hydroxy-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridin-6-ium bromide

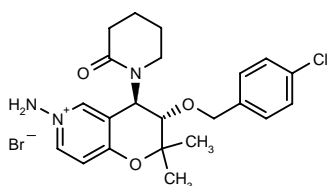


C₁₅ H₂₂ Br N₃ O₃; Mol wt: 372.2608

ACTION – Antihypertensive agent with increased potency as compared to cromakalim in lowering blood pressure in conscious normotensive rats at doses of 0.1-1.0 mg/kg p.o. and reported to cause less reflex tachycardia than cromakalim. Other compounds within this series of azacromakalim derivatives include the following:



Compound	R1	R2	Formula
276808	Me	H	C ₂₃ H ₂₈ N ₂ O ₃
276809	H	Cl	C ₂₂ H ₂₅ ClN ₂ O ₃



276807: C₂₂ H₂₇ Br Cl N₃ O₃

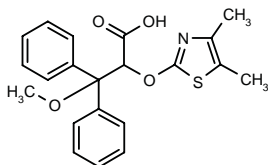
SOURCE – Egis.

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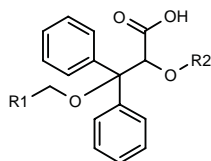
277020

2-(4,5-Dimethylthiazol-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid



C₂₁ H₂₁ N O₄ S; Mol wt: 383.4659

ACTION – Endothelin receptor antagonist with selectivity for ET_A receptors, as demonstrated in a binding assay by K_i values of 13 and 650 nM for ET_A and ET_B receptors, respectively. Potentially useful for the treatment of heart failure, restenosis, hypertension, pulmonary hypertension, renal disorders, cerebral ischemia, asthma, benign prostatic hyperplasia and prostatic cancer. Other compounds from this series of α -hydroxycarboxylic acid derivatives include the following:



Compound	R1	R2	Formula
277022	H	4,5-(Me) ₂ -2-oxazolyl	C ₂₁ H ₂₁ NO ₅
277023	H	5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl	C ₂₂ H ₂₁ NO ₄ S
277024	H	2-benzothiazolyl	C ₂₃ H ₁₉ NO ₄ S
277026	3,4-(MeO) ₂ -PhCH ₂	4,5-(Me) ₂ -2-thiazolyl	C ₃₀ H ₃₁ NO ₆ S
277027	3,4-(MeO) ₂ -PhCH ₂	4,5-(Me) ₂ -2-oxazolyl	C ₃₀ H ₃₁ NO ₇

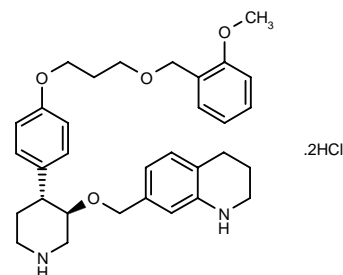
SOURCE – BASF.

REFERENCES

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277037

trans-7-[4-[4-[3-(2-Methoxybenzyloxy)propoxy]phenyl]-piperidin-3-yloxymethyl]-1,2,3,4-tetrahydroquinoline dihydrochloride



C₃₂ H₄₀ N₂ O₄ . 2HCl; Mol wt: 589.5998

ACTION – Potent, orally active human renin inhibitor (IC₅₀ = 37 and 0.67 nM against human plasma renin and recombinant human renin, respectively) proven to induce potent and long-lasting blood pressure reductions in sodium-depleted marmosets (maximum reduction of 19 mmHg at 3 mg/kg p.o. after 8.5 h). Compound exhibited improved aqueous solubility (> 3 mg/ml) and low lipophilicity as compared to other renin inhibitors.

SOURCE – Roche.

REFERENCES

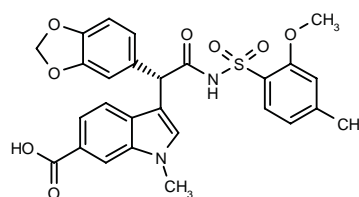
1. Binggeli, A. et al. (F. Hoffmann-La Roche AG) *New 4-(oxyalkoxyphenyl)-3-oxy-piperidines for treating heart and kidney insufficiency.* EP 863875, JP 99500447, WO 9709311.

2. Güller, R. et al. *Piperidine-renin inhibitors compounds with improved physicochemical properties.* Bioorg Med Chem Lett 1999, 9(10): 1403.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

276264

(+)-3-[1(S)-(1,3-Benzodioxol-5-yl)-2-(2-methoxy-4-methylphenylsulfonamido)-2-oxoethyl]-1-methyl-1*H*-indole-6-carboxylic acid



C₂₇ H₂₄ N₂ O₈ S; Mol wt: 536.5586

ACTION – Endothelin receptor antagonist for the treatment of restenosis, renal failure and pulmonary hypertension, the (+)-enantiomer of a previously reported compound*.

SOURCE – Pfizer.

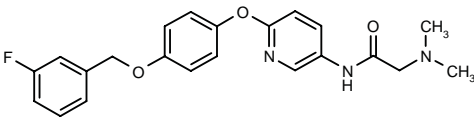
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*See **258983** Drug Data Report 1998, 020(03): 0222.

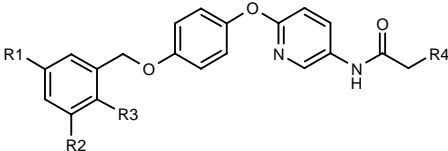
276555

2-(Dimethylamino)-N-[6-[4-(3-fluorobenzoyloxy)phenoxy]-3-pyridinyl]acetamide



C22 H22 F N3 O3; Mol wt: 395.4318

ACTION – Na⁺/Ca²⁺ exchange inhibitor (69% at 1 μM in endoplasmic reticulum of canine ventricular muscle preparations) with potential in the treatment of cardiac, cerebral and renal ischemic disorders. Other exemplified phenoxy pyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
276558	H	H	H	Cl	C ₂₀ H ₁₇ ClN ₂ O ₃
276560	F	H	F	Cl	C ₂₀ H ₁₅ ClF ₂ N ₂ O ₃
276562	H	H	H	1-pyrrolidinyl	C ₂₄ H ₂₅ N ₃ O ₃
276563	H	H	H	1-Pip	C ₂₆ H ₂₇ N ₃ O ₃
276565	H	H	H	4-OH-1-Pip	C ₂₆ H ₂₇ N ₃ O ₄
276566	H	H	H	4-thiomorpholinyl	C ₂₄ H ₂₅ N ₃ O ₃ S
276567	H	H	H	N(CH ₂ CH ₂ OH) ₂	C ₂₄ H ₂₇ N ₃ O ₅
276569	F	F	H	1-pyrrolidinyl	C ₂₄ H ₂₃ F ₂ N ₃ O ₃

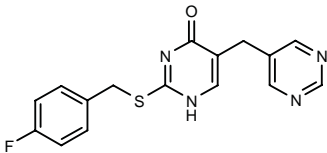
SOURCE – Taisho.

REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Phenoxy pyridine derivs*. JP 99092454.

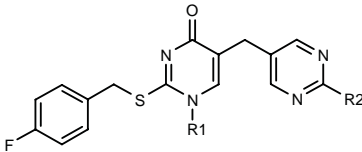
276878

2-(4-Fluorobenzylsulfanyl)-5-(5-pyrimidinylmethyl)-pyrimidin-4(1H)-one



C16 H13 F N4 O S; Mol wt: 328.3697

ACTION – An inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) expected to be useful in the treatment of atherosclerosis by virtue of its ability to inhibit the formation of lysophosphatidylcholine and oxidized free fatty acids. Also reported to be useful for the treatment of diabetes, hypertension, angina pectoris and other cardiovascular disorders, stroke, inflammatory disorders, Alzheimer’s disease, schizophrenia and psoriasis. Within this series of specifically claimed pyrimidinone derivatives, the following are also included:



Compound	R1	R2	Formula
276879	Me	H	C ₁₇ H ₁₅ FN ₄ OS
276880	CH ₂ CONHC14H ₂₉	H	C ₃₂ H ₄₄ FN ₅ O ₂ S
276881	CH ₂ CON(Me)C12H ₂₅	H	C ₃₁ H ₄₂ FN ₅ O ₂ S
276882	CH ₂ CON(Me)C12H ₂₅	OMe	C ₃₂ H ₄₄ FN ₅ O ₃ S

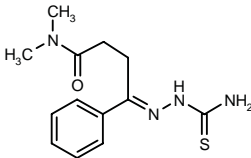
SOURCE – SmithKline Beecham.

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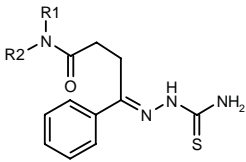
276950

N,N-Dimethyl-4-phenyl-4-(thiosemicarbazono)butyramide



C13 H18 N4 O S; Mol wt: 278.3782

ACTION – Antiatherosclerotic agent that acts by increasing plasma HDL cholesterol levels, as demonstrated *in vivo* in cholesterol-fed rats where it produced a 56.2% increase in HDL cholesterol when given at 50 mg/kg/day p.o. mixed with the diet. Other specifically claimed compounds from this series of 4-[(amino-thioxomethyl)hydrazono]-4-arylbutanamides include the following:



Compound	R1	R2	Formula
276951	Bu	H	C ₁₅ H ₂₂ N ₄ OS
276952	H	H	C ₁₁ H ₁₄ N ₄ OS
276953	CH2Ph	H	C ₁₈ H ₂₀ N ₄ OS
276954	Me	H	C ₁₂ H ₁₆ N ₄ OS
276955	cyclohexyl	H	C ₁₇ H ₂₄ N ₄ OS
276956	i-Pr	H	C ₁₄ H ₂₀ N ₄ OS
276957	-(CH2)5-		C ₁₆ H ₂₂ N ₄ OS
276958	i-BuCH2CH2CH(Me)	H	C ₁₉ H ₃₀ N ₄ OS

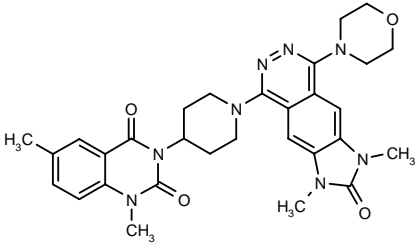
SOURCE – American Home Products.

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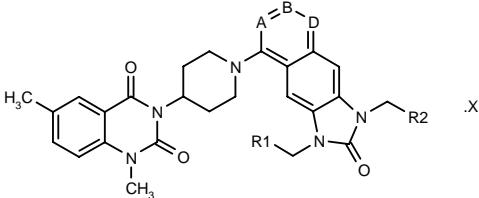
277244

3-[1-[1,3-Dimethyl-8-(4-morpholinyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-g]phthalazin-5-yl]piperidin-4-yl]-1,6-dimethylquinazoline-2,4(1H,3H)-dione

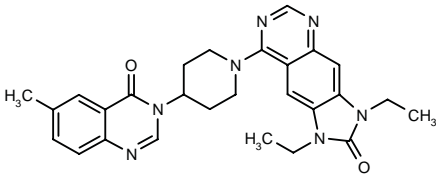


C30 H34 N8 O4; Mol wt: 570.6506

ACTION – Adenosine reuptake inhibitor, as demonstrated by inhibition of [³H]-adenosine uptake in human erythrocytes (IC₅₀ = 15 nM), with potential in the treatment of myocardial ischemia, renal disorders, pancreatitis and foot edema. Other compounds from this series of piperidine derivatives include the following:



Compound	R1	R2	A	B	D	X	Formula
277245	H	Me	N	CH	N		C ₂₇ H ₂₉ N ₇ O ₃
277247	H	H	N	N	CH		C ₂₆ H ₂₇ N ₇ O ₃
277248	Me	Me	N	N	CH		C ₂₈ H ₃₁ N ₇ O ₃
277249	Me	Me	N	N	C[N(Pr)2]	HCl	C ₃₄ H ₄₄ N ₈ O ₃ .HCl
277250	Me	Me	CH	CH	N		C ₂₉ H ₃₂ N ₆ O ₃



277246: C27 H29 N7 O2

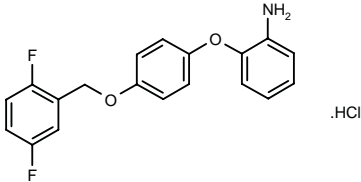
SOURCE – Kyowa Hakko.

REFERENCES

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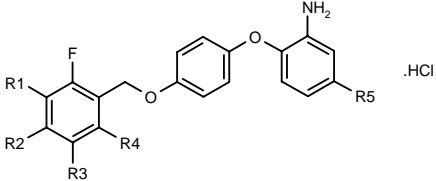
277290

2-[4-(2,5-Difluorobenzyloxy)phenoxy]aniline hydrochloride



C19 H15 F2 N O2 . HCl; Mol wt: 363.7894

ACTION – Agent for the treatment of cardiac, cerebral and renal ischemic disorders that acts by inhibiting Na⁺/Ca²⁺ exchange. A representative compound from a series of 2-phenoxyaniline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
277291	F	H	H	H	H	C ₁₉ H ₁₅ F ₂ NO ₂ .HCl
277292	H	H	H	F	H	C ₁₉ H ₁₅ F ₂ NO ₂ .HCl
277293	H	H	F	H	OEt	C ₂₁ H ₁₉ F ₂ NO ₃ .HCl
277294	H	H	H	F	OEt	C ₂₁ H ₁₉ F ₂ NO ₃ .HCl
277295	H	F	H	H	H	C ₁₉ H ₁₅ F ₂ NO ₂ .HCl
277296	F	H	H	H	OEt	C ₂₁ H ₁₉ F ₂ NO ₃ .HCl

SOURCE – Taisho.

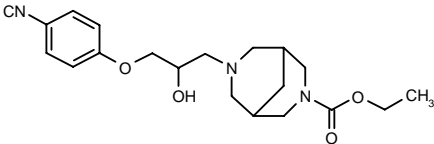
REFERENCES

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ANTIARRHYTHMIC DRUGS

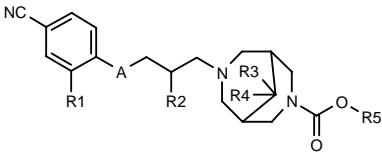
278133

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester

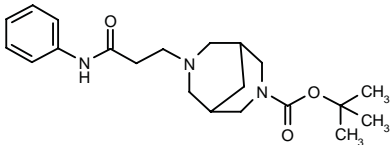


C20 H27 N3 O4; Mol wt: 373.4503

ACTION – Antiarrhythmic agent found to exert short-lasting class III electrophysiological activity and therefore expected to be useful in the treatment of cardiac arrhythmias, in particular atrial and ventricular arrhythmias. Other representative compounds from this series of bispidine derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
278134	cyclopropyl-NHCO	OH	H	H	t-Bu	O	C ₂₆ H ₃₆ N ₄ O ₅
278136	H	H	H	H	t-Bu	CH(OH)	C ₂₃ H ₃₃ N ₃ O ₃
278137	H	OH	-(CH2)4-		t-Bu	O	C ₂₆ H ₃₇ N ₃ O ₄
278138	H	OH	H	H	Pr	O	C ₂₁ H ₂₉ N ₃ O ₄
278139	H	OH	Me	Me	t-Bu	O	C ₂₄ H ₃₅ N ₃ O ₄



278135: C21 H31 N3 O3

SOURCE – AstraZeneca.

REFERENCES

1. Strandlund, G. et al. (Astra AB) *Novel bispidine antiarrhythmic cpds.* WO 9931100.

HEART FAILURE THERAPY

COLFORSIN DAPROPATE

Rec INNM

133606

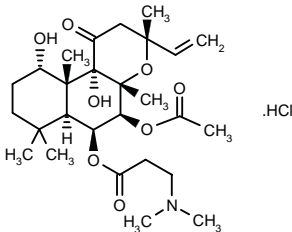
6-O-[3-(Dimethylamino)propionyl]forskolin hydrochloride

(+)-(3*R*,4*aR*,5*S*,6*S*,6*aS*,10*S*,10*aR*,10*bS*)-5-Acetoxy-6-[3-(dimethylamino)propionyloxy]-10,10*b*-dihydroxy-3,4*a*,7,7,10*a*-pentamethyl-3-vinyldodecahydro-1*H*-naphtho[2,1-*b*]pyran-1-one hydrochloride

7β-Acetoxy-6β-[3-(dimethylamino)propionyloxy]-1α,9α-dihydroxylabd-14-en-11-one hydrochloride

N,N-Dimethyl-β-alanine [3*R*-(3α,4αβ,5β,6β,6αα,10α,10αβ,10*b*α)]-5-(acetyloxy)-3-ethenyldodecahydro-10,10*b*-dihydroxy-3,4*a*,7,7,10*a*-pentamethyl-1-oxo-1*H*-naphtho[2,1-*b*]pyran-6-yl ester hydrochloride

Colforsin daproate hydrochloride
NKH-477⁺



C27 H43 N O8 . HCl; Mol wt: 546.1070

ACTION – Cardiotonic agent.

INDICATIONS – Treatment of acute heart failure.

PRESENTATION – Vials, lyophilized powder for reconstitution in physiological saline solution or water for i.v. drip infusion, 5 and 10 mg.

PROPRIETARY NAME – Adehl (JP).

SOURCE – Nippon Kayaku.

RECENT REFERENCES

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2. Himeta, M. et al. *Characterization of the vasodilating effects of NKH477, a novel forskolin derivative, in isolated rat aortae, canine arteries and rabbit femoral arteries and veins.* Jpn Pharmacol Ther 1998, 26(5): 129.

3. Hosoda, S. et al. *Acute effect of NKH477, a novel forskolin derivative, in patients with acute heart failure: A multicenter placebo-controlled double-blind trial.* Jpn J Clin Pharmacol Ther 1997, 28(2): 583.

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7. Irie, T. et al. *Metabolic fate of NKH477 (3): Feto-placental transfer and excretion into milk in rats after a single intravenous administration.* Xenobiotic Metab Dispos 1998, 13(3): 229.

8. Irie, T. et al. *Metabolic fate of NKH477 (4): Metabolism after intravenous administration in rats, dogs and human*. Xenobiotic Metab Dispos 1998, 13(3): 237.

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10. Maeda, H. et al. *Potential antidepressant properties of forskolin and a novel water-soluble forskolin (NKH477) in the forced swimming test*. Life Sci 1997, 61(25): 2435.

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16. Onda, T. and Hosono, M. *Effectiveness of NKH477 in the isolated guinea-pig heart with contractile dysfunction following post-ischemic reperfusion*. Jpn Pharmacol Ther 1998, 26(9): 173.

17. Ozawa, H. et al. *Novel water soluble forskolin analog (NKH477) shows antidepressant like effects in forced swim test*. Biol Psychiatry 1997, 42(1, Suppl.): Abst 90-3.

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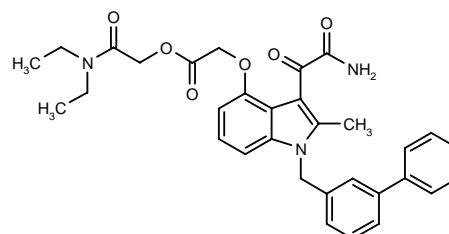
MONOGRAPH – Prous, J. and Castañer, J. *NKH-477*. Drugs Fut 1993, 018(02): 0134.

*Drug Data Rep 1990, 012(06): 0459.

TREATMENT OF SHOCK

276405

2-[3-(2-Amino-2-oxoacetyl)-1-(biphenyl-3-ylmethyl)-2-methyl-1H-indol-4-yloxy]acetic acid diethylcarbamoylmethyl ester



C32 H33 N3 O6; Mol wt: 555.6277

ACTION – *N,N*-Diethylglycolamido ester prodrug of a known human nonpancreatic secretory phospholipase A₂ (sPLA₂) inhibitor with highly improved oral bioavailability compared to other ester prodrugs. Potentially useful for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

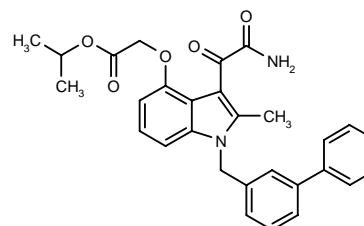
SOURCE – Lilly.

REFERENCES

1. Denney, M.L. et al. (Eli Lilly and Company) *N,N*-Diethylglycolamido ester prodrugs of indole sPLA₂ inhibitors. WO 9921546.

276408

2-[3-(2-Amino-2-oxoacetyl)-1-(biphenyl-3-ylmethyl)-2-methyl-1H-indol-4-yloxy]acetic acid isopropyl ester



C29 H28 N2 O5; Mol wt: 484.5492

ACTION – Isopropyl ester prodrug of a known human nonpancreatic secretory phospholipase A₂ (sPLA₂) inhibitor with highly improved oral bioavailability compared to other ester prodrugs. Potentially useful for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

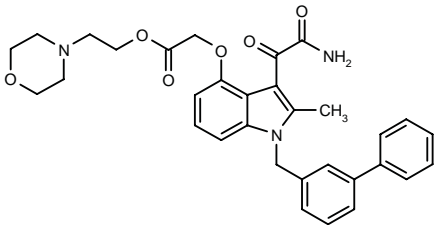
SOURCE – Lilly.

REFERENCES

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276410

2-[3-(2-Amino-2-oxoacetyl)-1-(biphenyl-3-ylmethyl)-2-methyl-1*H*-indol-4-yloxy]acetic acid 2-(morpholin-4-yl)-ethyl ester



C32 H33 N3 O6; Mol wt: 555.6277

ACTION – Morpholino-*N*-ethyl ester prodrug of a known human nonpancreatic secretory phospholipase A₂ (sPLA₂) inhibitor with highly improved oral bioavailability compared to other ester prodrugs. Potentially useful for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

SOURCE – Lilly.

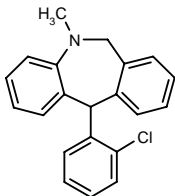
REFERENCES

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MISCELLANEOUS
CARDIOVASCULAR DRUGS

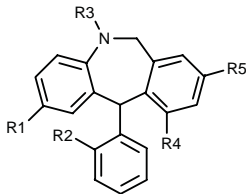
277090

11-(2-Chlorophenyl)-5-methyl-6,11-dihydro-5*H*-dibenzo[*b,e*]azepine



C21 H18 Cl N; Mol wt: 319.8332

ACTION – Potent and selective inhibitor of the Ca²⁺-activated potassium channel (also known as the Gardos channel) of erythrocytes and of mitogen-induced mammalian cell proliferation, with potential in the treatment of sickle cell disease and disorders characterized by abnormal or unwanted cell proliferation such as cancer, blood vessel proliferation disorders, fibrotic disorders, arteriosclerosis and dermatological disorders. *In vitro*, compound inhibited the Gardos channel with an IC₅₀ value of 0.414-0.433 μM; in addition, it was shown to inhibit mitogen-induced proliferation of murine fibroblast NIH3T3 cells with an IC₅₀ value of 0.800 μM. Compound is also reported to inhibit chloride secretion in intestinal cells and thus may be useful for the treatment of diarrhea and scours. A representative compound from a series of substituted 11-phenyldibenzazepine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
277091	H	H	Me	H	H	C ₂₁ H ₁₉ N
277092	H	Cl	H	H	H	C ₂₀ H ₁₆ ClN
277093	H	H	CO ₂ Me	H	H	C ₂₂ H ₁₉ NO ₂
277095	H	Cl	CO ₂ Me	H	H	C ₂₂ H ₁₈ ClNO ₂
277096	H	H	CO ₂ Ph	H	H	C ₂₇ H ₂₁ NO ₂
277097	H	Cl	CO ₂ Ph	H	H	C ₂₇ H ₂₀ ClNO ₂
277098	H	Cl	4-NO ₂ -PhCO	H	H	C ₂₇ H ₁₉ ClN ₂ O ₃
277099	Cl	Cl	4-NO ₂ -PhCO	H	OMe	C ₂₈ H ₂₀ Cl ₂ N ₂ O ₄
277100	Cl	Cl	4-NO ₂ -PhCO	OMe	H	C ₂₈ H ₂₀ Cl ₂ N ₂ O ₄
277101	H	Cl	4-NO ₂ -PhNHCO	H	H	C ₂₇ H ₂₀ ClN ₃ O ₃

SOURCES – Children’s Medical Center, Cambridge, MA (US); Harvard College, Cambridge, MA (US); Ion Pharmaceuticals.

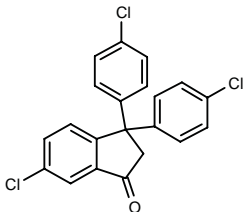
REFERENCES

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2. Brugnara, C. et al. (Harvard College;Ion Pharmaceuticals, Inc.;Children’s Medical Center Corp.) *Use of substd. 11-phenyl-dibenzazepine cpds. for the treatment or prevention of sickle cell disease, inflammatory diseases characterized by abnormal cell proliferation, diarrhea and scour*. WO 9926628.

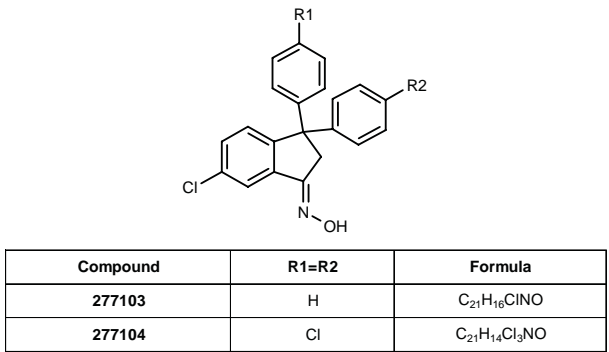
277102

6-Chloro-3,3-bis(4-chlorophenyl)indan-1-one



C21 H13 Cl3 O; Mol wt: 387.6917

ACTION – Potent and selective inhibitor of the erythrocyte Ca²⁺-activated potassium channel (Gardos channel) and of mammalian cell proliferation, and thereby useful for the treatment of sickle cell disease and also for diseases characterized by abnormal cell proliferation. It gave an IC₅₀ of 0.176 μM in a Gardos channel assay and of 2.0 μM in a mitogenic assay in murine fibroblast NIH3T3 cells. Compound also inhibited the proliferation of certain cancer cell lines (cervical CaSki, breast MCF-7, lung A549, hepatocellular HepG2 and colon HT29 cells) with IC₅₀ values of 5.5-8.9 μM. Other representative compounds within this series of substituted 3,3-diphenyl indanones, indanes and indoles include the following:



SOURCES – Children’s Medical Center, Cambridge, MA (US); Harvard College, Cambridge, MA (US); Ion Pharmaceuticals.

REFERENCES

1. Brugnara, C. et al. (Harvard College;Children's Medical Center Corp.;Ion Pharmaceuticals, Inc.) *Substd. diphenyl indanone, indane and indole cpds. and analogues thereof useful for the treatment or prevention of diseases characterized by abnormal cell proliferation.* WO 9926611.

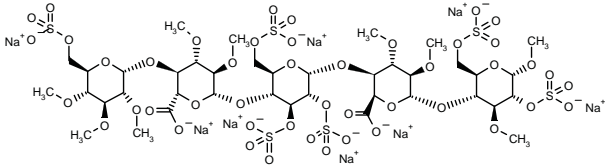
2. Brugnara, C. et al. (Harvard College;Children's Medical Center Corp.;Ion Pharmaceuticals, Inc.) *Use of substd. diphenyl indanone, indane and indole cpds. for the treatment or prevention of sickle cell disease, inflammatory diseases characterized by abnormal cell proliferation, diarrhea and scours.* WO 9926624.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

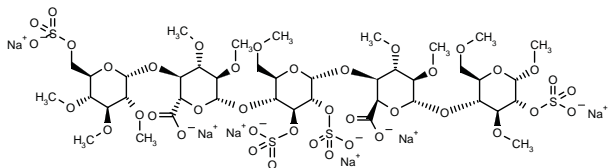
277000

O-(2,3,4-Tri-*O*-methyl-6-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,3-*O*-dimethyl- β -D-glucopyranosyluronic acid)-(1 \rightarrow 4)-*O*-(2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,3-*O*-dimethyl- α -L-idopyranosyluronic acid)(1 \rightarrow 4)-1,3-di-*O*-methyl-2,6-di-*O*-sulfo- α -D-glucopyranose octasodium salt

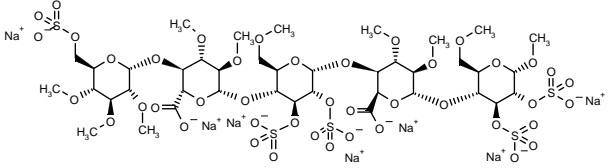


C39 H58 Na8 O46 S6; Mol wt: 1639.1570

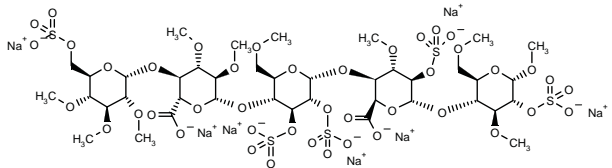
ACTION – Anticoagulant with factor Xa-inhibitory activity (IC₅₀ < 2 μ mol/l), reported to exhibit fewer side effects as compared to previously disclosed pentasaccharide derivatives such as lower bleeding risks and absence of heparin-induced thrombocytopenia due to its lower sulfate content. Compound is reported to be suitable for once-a-day administration. Also useful as an inhibitor of smooth muscle proliferation and for the treatment of cancer, angiogenesis and retrovirus infections. Other exemplified compounds from this series of carbohydrate derivatives include the following:



277001: C41 H64 Na6 O40 S4



277008: C40 H61 Na7 O43 S5



277009: C41 H63 Na7 O42 S5

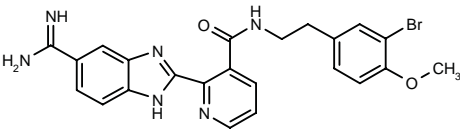
SOURCES – Akzo Nobel; Sanofi-Synthélabo.

REFERENCES

1. Van Boeckel, C.A.A. et al. (Akzo Nobel N.V.;Sanofi SA) *Carbohydrate derivs.* WO 9925720.

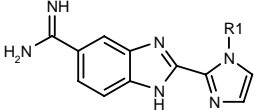
277111

2-(5-Amidino-1*H*-benzimidazol-2-yl)-*N*-[2-(3-bromo-4-methoxyphenyl)ethyl]pyridine-3-carboxamide

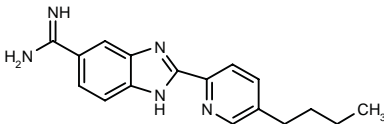


C23 H21 Br N6 O2; Mol wt: 493.3629

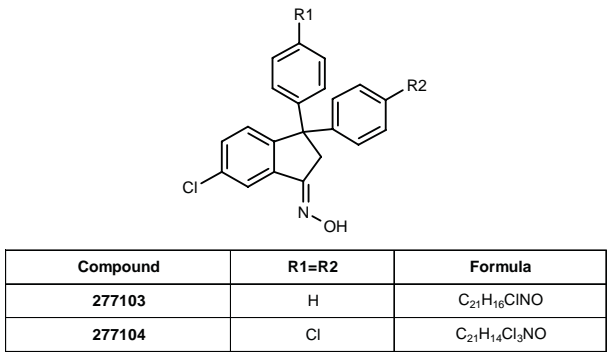
ACTION – Anticoagulant, a factor Xa inhibitor (K_i = 0.002 μ M for human factor Xa) reported to increase the activated clotting time (ACT) both *in vitro* and *ex vivo* in rabbit blood. Other exemplified substituted amidinoaryl derivatives include the following:



Compound	R1	Formula
277113	CH2Ph	C ₁₈ H ₁₆ N ₆
277114	4-Cl-PhCH2CH2NHCOCH2	C ₂₁ H ₂₀ ClN ₇ O
277115	4-morpholinyl-CO(CH2)3	C ₁₉ H ₂₃ N ₇ O ₂



277112: C17 H19 N5



SOURCES – Children’s Medical Center, Cambridge, MA (US); Harvard College, Cambridge, MA (US); Ion Pharmaceuticals.

REFERENCES

1. Brugnara, C. et al. (Harvard College;Children's Medical Center Corp.;Ion Pharmaceuticals, Inc.) *Substd. diphenyl indanone, indane and indole cpds. and analogues thereof useful for the treatment or prevention of diseases characterized by abnormal cell proliferation.* WO 9926611.

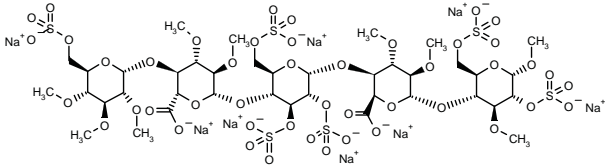
2. Brugnara, C. et al. (Harvard College;Children's Medical Center Corp.;Ion Pharmaceuticals, Inc.) *Use of substd. diphenyl indanone, indane and indole cpds. for the treatment or prevention of sickle cell disease, inflammatory diseases characterized by abnormal cell proliferation, diarrhea and scours.* WO 9926624.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

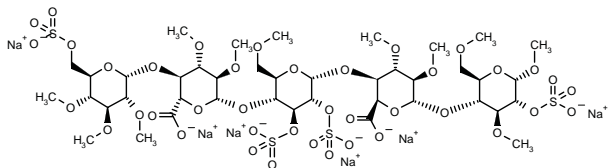
277000

O-(2,3,4-Tri-*O*-methyl-6-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,3-*O*-dimethyl- β -D-glucopyranosyluronic acid)-(1 \rightarrow 4)-*O*-(2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,3-*O*-dimethyl- α -L-idopyranosyluronic acid)(1 \rightarrow 4)-1,3-di-*O*-methyl-2,6-di-*O*-sulfo- α -D-glucopyranose octasodium salt

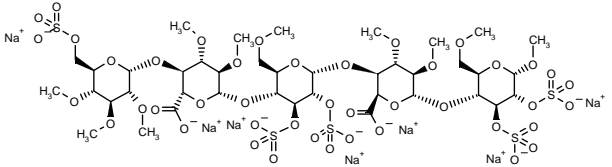


C39 H58 Na8 O46 S6; Mol wt: 1639.1570

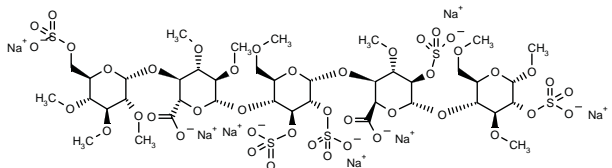
ACTION – Anticoagulant with factor Xa-inhibitory activity (IC₅₀ < 2 μ mol/l), reported to exhibit fewer side effects as compared to previously disclosed pentasaccharide derivatives such as lower bleeding risks and absence of heparin-induced thrombocytopenia due to its lower sulfate content. Compound is reported to be suitable for once-a-day administration. Also useful as an inhibitor of smooth muscle proliferation and for the treatment of cancer, angiogenesis and retrovirus infections. Other exemplified compounds from this series of carbohydrate derivatives include the following:



277001: C41 H64 Na6 O40 S4



277008: C40 H61 Na7 O43 S5



277009: C41 H63 Na7 O42 S5

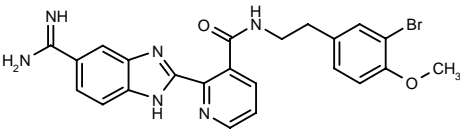
SOURCES – Akzo Nobel; Sanofi-Synthélabo.

REFERENCES

1. Van Boeckel, C.A.A. et al. (Akzo Nobel N.V.;Sanofi SA) *Carbohydrate derivs.* WO 9925720.

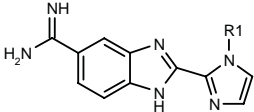
277111

2-(5-Amidino-1*H*-benzimidazol-2-yl)-*N*-[2-(3-bromo-4-methoxyphenyl)ethyl]pyridine-3-carboxamide

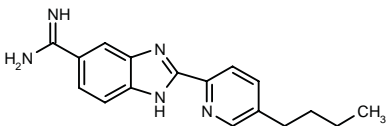


C23 H21 Br N6 O2; Mol wt: 493.3629

ACTION – Anticoagulant, a factor Xa inhibitor (K_i = 0.002 μ M for human factor Xa) reported to increase the activated clotting time (ACT) both *in vitro* and *ex vivo* in rabbit blood. Other exemplified substituted amidinoaryl derivatives include the following:



Compound	R1	Formula
277113	CH2Ph	C ₁₈ H ₁₆ N ₆
277114	4-Cl-PhCH2CH2NHCOCH2	C ₂₁ H ₂₀ ClN ₇ O
277115	4-morpholinyl-CO(CH2)3	C ₁₉ H ₂₃ N ₇ O ₂



277112: C17 H19 N5

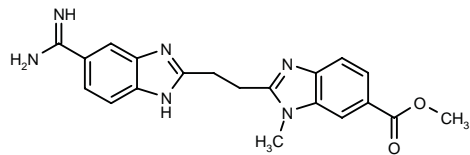
SOURCE – AxyS Pharmaceuticals.

REFERENCES

1. Fatheree, P.R. et al. (AxyS Pharmaceuticals, Inc.) *Substd. amidinoaryl derivs. and their use as anticoagulants*. WO 9926941.

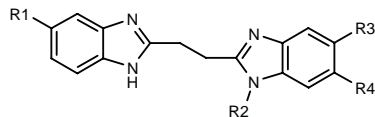
277120

2-[2-(5-Amidino-1*H*-benzimidazol-2-yl)ethyl]-1-methyl-1*H*-benzimidazole-6-carboxylic acid methyl ester

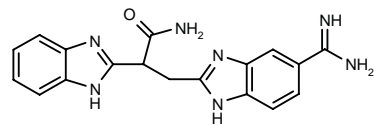


C20 H20 N6 O2; Mol wt: 376.4180

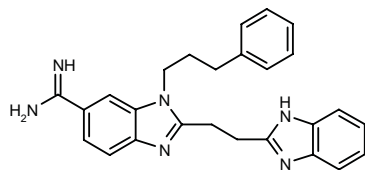
ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of human factor Xa ($K_i = 0.02$ nM). Other specifically claimed compounds from this series of substituted amidinoaryl derivatives include the following:



Compound	R1	R2	R3	R4	Formula
277121	C(=NH)NH2	H	H	CONH-CH2Ph	C ₂₅ H ₂₃ N ₇ O
277123	1-imidazolyl	H	C(=NH)NH2	H	C ₁₈ H ₁₈ N ₈
277124	C(=NH)NH2	Me	H	CO2H	C ₁₉ H ₁₈ N ₆ O ₂
277125	C(=NH)NH2	CH2Ph	H	H	C ₂₄ H ₂₂ N ₆
277127	C(=NH)NH2	H	-CO-D,L-Val-OH	H	C ₂₃ H ₂₅ N ₇ O ₃
277128	CO2H	H	C(=NH)NH2	H	C ₁₈ H ₁₈ N ₆ O ₂
277129	C(=NH)NH2	H	-CO-D,L-Glu-OH	H	C ₂₃ H ₂₃ N ₇ O ₅
277130	C(=NH)NH2	H	-CO-(3-Me)-D,L-Lys-OH	H	C ₂₅ H ₃₀ N ₆ O ₃
277131	C(=NH)NH2	H	-CO-D,L-Ala-OH	H	C ₂₁ H ₂₁ N ₇ O ₃
277132	C(=NH)NH2	H	-CO-D,L-Phe-OH	H	C ₂₇ H ₂₅ N ₇ O ₃



277122: C18 H17 N7 O



277126: C26 H26 N6

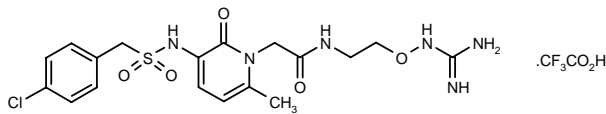
SOURCE – AxyS Pharmaceuticals.

REFERENCES

1. Day, R.F. and Young, W.B. (AxyS Pharmaceuticals, Inc.) *Substd. amidinoaryl derivs. and their use as anticoagulants*. WO 9926933.

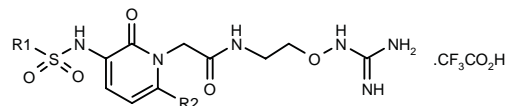
277176

2-[3-(4-Chlorobenzylsulfonamido)-6-methyl-2-oxo-1,2-dihydropyridin-1-yl]-*N*-[2-(guanidinoxy)ethyl]acetamide trifluoroacetate

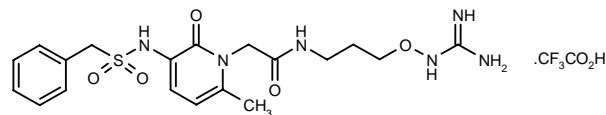


C18 H23 Cl N6 O5 S . C2 H F3 O2; Mol wt: 584.9576

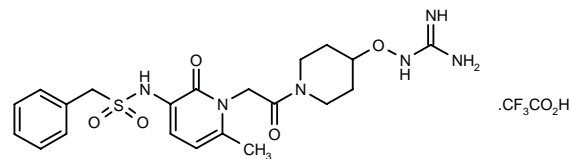
ACTION – Anticoagulant and antithrombotic agent, a potent thrombin inhibitor ($K_i = 2.0$ nM) with high selectivity relative to other serine proteases such as factor Xa ($K_i = 2.2$ μ M), elastase (0% inhibition at 19 μ M) and trypsin ($K_i = 4$ μ M). Other exemplified compounds from this series of heteroaryl aminoguanidines and alkoxyguanidines include the following:



Compound	R1	R2	Formula
277178	CH2Ph	Me	C ₁₈ H ₂₄ N ₆ O ₅ S.C ₂ HF ₃ O ₂
277180	CH2Ph	H	C ₁₇ H ₂₂ N ₆ O ₅ S.C ₂ HF ₃ O ₂
277181	3-Me-Ph	Me	C ₁₈ H ₂₄ N ₆ O ₅ S.C ₂ HF ₃ O ₂
277183	3,4-(Cl)2-PhCH2	Me	C ₁₈ H ₂₂ Cl ₂ N ₆ O ₅ S.C ₂ HF ₃ O ₂
277185	2-Cl-Ph	Me	C ₁₇ H ₂₁ ClN ₆ O ₅ S.C ₂ HF ₃ O ₂
277186	4-I-Ph	Me	C ₁₇ H ₂₁ IN ₆ O ₅ S.C ₂ HF ₃ O ₂
277187	5-Br-2-MeO-Ph	Me	C ₁₈ H ₂₃ BrN ₆ O ₆ S.C ₂ HF ₃ O ₂
277188	2-NO2-Ph	Me	C ₁₈ H ₂₁ N ₇ O ₅ S.C ₂ HF ₃ O ₂
277190	6-Cl-2-Naph	Me	C ₂₁ H ₂₃ ClN ₆ O ₅ S.C ₂ HF ₃ O ₂



277177: C19 H26 N6 O5 S . C2 H F3 O2



277182: C21 H28 N6 O5 S . C2 H F3 O2

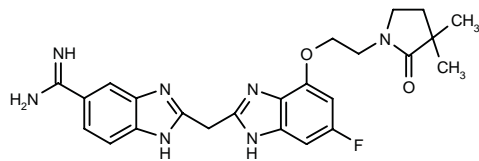
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Lu, T. et al. (3-Dimensional Pharmaceuticals, Inc.) *Heteroaryl aminoguanidines and alkoxyguanidines and their use as protease inhibitors*. WO 9926926.

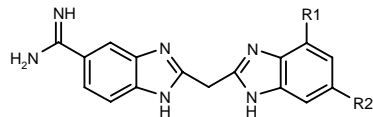
277209

2-[4-[2-(3,3-Dimethyl-2-oxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzimidazol-2-ylmethyl]-1*H*-benzimidazole-5-carboxamide



C24 H26 F N7 O2; Mol wt: 463.5144

ACTION – Anticoagulant, a factor Xa inhibitor ($K_i = 0.005 \mu\text{M}$) that doubled the activated clotting time (ACT) in rabbit and human blood *in vitro* at concentrations of 8 and 9 μM , respectively. Compound is also reported to be active in doubling ACT *ex vivo* in rabbit blood. Other specifically claimed biheterocyclic compounds include the following:



Compound	R1	R2	Formula
277210	OCH2CH2OCH2CH2OMe	H	C ₂₁ H ₂₄ N ₆ O ₃
277211	1,3-benzodioxol-5-yl-CH2O	F	C ₂₄ H ₁₉ FN ₆ O ₃
277212	phthalimido-CH2CH2O	F	C ₂₆ H ₂₀ FN ₇ O ₃
277213	1-Pip-CH2CH2NHSO2	Cl	C ₂₃ H ₂₇ ClN ₆ O ₂ S
277214	F	F	C ₁₆ H ₁₂ F ₂ N ₆

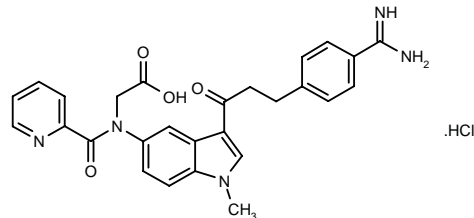
SOURCE – AxyS Pharmaceuticals.

REFERENCES

1. Fatheree, P.R. et al. (AxyS Pharmaceuticals, Inc.) *By amidino group substd. heterocyclic derivs. and their use as anticoagulants.* WO 9926932.

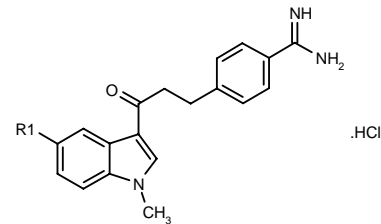
277356

N-[3-[3-(4-Amidinophenyl)propionyl]-1-methyl-1*H*-indol-5-yl]-*N*-(pyridin-2-ylcarbonyl)glycine hydrochloride



C27 H25 N5 O4 . HCl; Mol wt: 519.9864

ACTION – Antithrombotic agent, an inhibitor of thrombin also reported to inhibit other serine proteases and to act as a fibrinogen receptor antagonist. *In vitro*, compound was shown to double the thrombin time in human plasma at a concentration of 0.048 μM . Other exemplified compounds from this series of substituted indoles include the following:



Compound	R1	Formula
277357	CON(Ph)CH2CH2CO2H	C ₂₉ H ₂₈ N ₄ O ₄ .HCl
277358	N(4-thiazolyl-CO)CH2CO2H	C ₂₅ H ₂₃ N ₅ O ₄ S.HCl

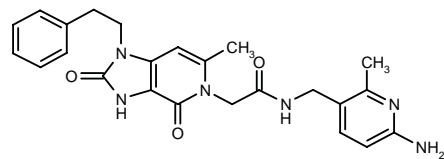
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Heckel, A. et al. (Boehringer Ingelheim Pharma KG) *Subst. indoles, having a thrombin inhibiting effect.* WO 9928297.

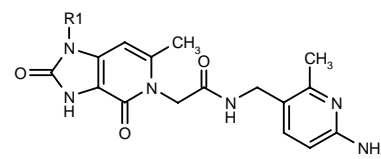
277365

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[6-methyl-2,4-dioxo-1-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-5-yl]acetamide

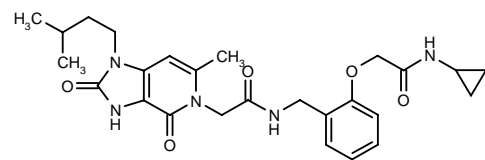


C24 H26 N6 O3; Mol wt: 446.5084

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human thrombin ($K_i < 10 \text{ nM}$). Other specifically claimed compounds from this series of 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-imidazo[4,5-*c*]pyridine derivatives include the following:



Compound	R1	Formula
277366	2-Pyr-CH2CH2	C ₂₃ H ₂₅ N ₇ O ₃
277367	cyclohexyl-CH2	C ₂₃ H ₃₀ N ₆ O ₃
277368	t-BuCH2CH2	C ₂₂ H ₃₀ N ₆ O ₃
277369	CH(Me)Ph	C ₂₄ H ₂₆ N ₆ O ₃
277370	cyclopropyl	C ₁₉ H ₂₂ N ₆ O ₃
277371	i-BuCH2	C ₂₁ H ₂₈ N ₆ O ₃



277372: C25 H32 N6 O5

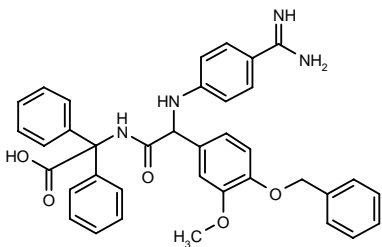
SOURCE – Merck & Co.

REFERENCES

1. Coburn, C. (Merck & Co., Inc.) *Thrombin inhibitors.* WO 9927930.

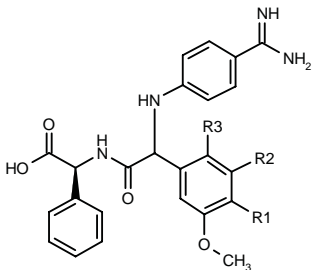
277452

2-[2-(4-Amidinophenylamino)-2-(4-benzyloxy-3-methoxyphenyl)acetamido]-2,2-diphenylacetic acid

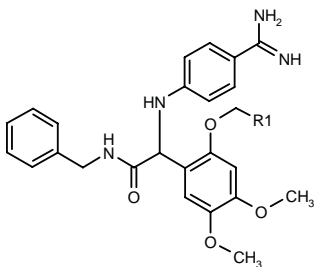


C37 H34 N4 O5; Mol wt: 614.6986

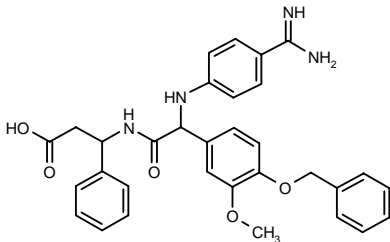
ACTION – A factor VIIa/tissue factor inhibitor with potential in the treatment of thrombosis, stroke, myocardial infarction, inflammation and arteriosclerosis, also reported to be useful as an antitumor agent. Other specifically claimed compounds from this series of *N*-(4-amidinophenylamino)phenylglycinamide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
277454	OCH2Ph	H	H	R	C ₃₁ H ₃₀ N ₄ O ₅
277455	H	OMe	H	S	C ₂₅ H ₂₆ N ₄ O ₅
277458	OCH2Ph	H	NHSO2Ph	R	C ₃₇ H ₃₅ N ₅ O ₇ S
277459	OCH2Ph	H	NHSO2Ph	S	C ₃₇ H ₃₅ N ₅ O ₇ S
277460	OCH2Ph	H	NHCOCH2Ph	R	C ₃₉ H ₃₇ N ₅ O ₆
277461	OCH2Ph	H	NHCOCH2Ph	S	C ₃₉ H ₃₇ N ₅ O ₆



Compound	R1	Formula
277456	3-CO2H-Ph	C ₃₁ H ₃₀ N ₄ O ₆
277457	CO2H	C ₂₆ H ₂₈ N ₄ O ₆



277453: C32 H32 N4 O5

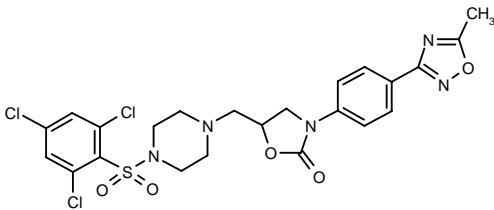
SOURCE – Roche.

REFERENCES

1. Gröbke, K. et al. (F. Hoffmann-La Roche AG) *N*-(4-Carbamimido-phenyl)-glycine amide derivs. EP 921116.

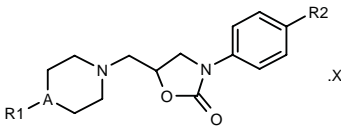
278126

3-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-5-[4-(2,4,6-trichlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one

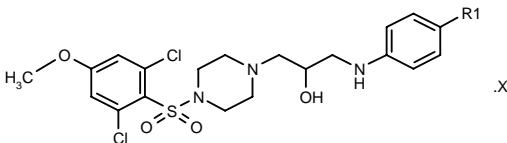


C23 H22 Cl3 N5 O5 S; Mol wt: 586.8818

ACTION – Anticoagulant, a factor Xa inhibitor potentially useful for the treatment and/or prevention of thromboembolic disorders. Other representative compounds from this series of benzamidine derivatives include the following:



Compound	R1	R2	A	X	Formula
278127	2,4,6-(Cl)3-PhSO2	C(=NH)NH2	N	acetate	C ₂₁ H ₂₂ Cl ₃ N ₅ O ₄ S .C ₂ H ₄ O ₂
278130	t-BuOCONH	5-Me-1,2,4-oxadiazol-3-yl	CH		C ₂₃ H ₃₁ N ₅ O ₅
278131	Ph	5-Me-1,2,4-oxadiazol-3-yl	N		C ₂₃ H ₂₅ N ₅ O ₃
278132	CONHBu	5-Me-1,2,4-oxadiazol-3-yl	N		C ₂₂ H ₃₀ N ₅ O ₄



Compound	R1	X	Formula
278128	5-Me-1,2,4-oxadiazol-3-yl		C ₂₃ H ₂₇ Cl ₂ N ₅ O ₅ S
278129	C(=NH)NH2	acetate	C ₂₁ H ₂₇ Cl ₂ N ₅ O ₄ S .C ₂ H ₄ O ₂

SOURCE – Merck KGaA.

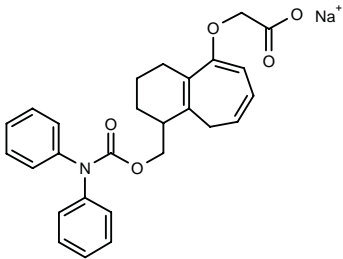
REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Benzamine derivs.* WO 9931092.

ANTIPLATELET THERAPY

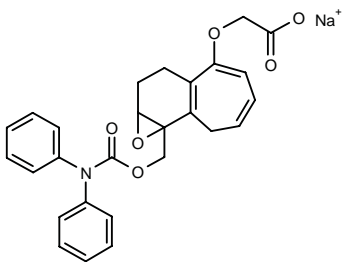
276779

2-[6-(*N,N*-Diphenylcarbamoyloxymethyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-1-yloxy]acetic acid sodium salt



C26 H24 N Na O5; Mol wt: 453.4676

ACTION – PGI₂ agonist shown to inhibit ADP-induced human platelet aggregation by over 90% at a concentration of 0.1 μM. Potentially useful for preventing arterial obstruction, restenosis or ischemic complications following coronary angioplasty, arteriosclerosis, cerebrovascular disorders, ischemic heart disease or dermatosis. Another exemplified benzocycloheptene derivative is:



276780: C27 H24 N Na O6

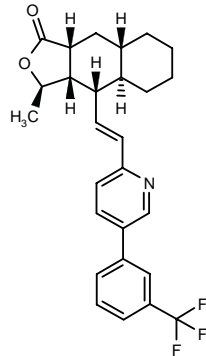
SOURCE – Fujisawa.

REFERENCES

1. Hattori, K. and Tanaka, A. (Fujisawa Pharmaceutical Co., Ltd.) *Benzocycloheptene derivs.* WO 9924397.

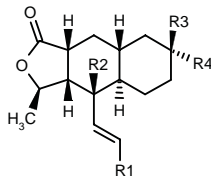
277142

(3*R*,3*aS*,4*R*,4*aR*,8*aS*,9*aR*)-3-Methyl-4-[(*E*)-2-[5-[3-(trifluoromethyl)phenyl]pyridin-2-yl]vinyl]perhydronaphtho[2,3-*c*]furan-1-one

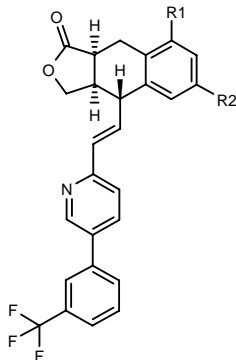


C27 H28 F3 N O2; Mol wt: 455.5172

ACTION – Thrombin receptor antagonist with potential in the treatment of thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, arrhythmia, heart failure, myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolic stroke, cerebral ischemia, peripheral vascular diseases, inflammatory disorders and cancer. Other specifically claimed compounds within this series of heterocyclic-substituted tricyclic derivatives include the following:



Compound	R1	R2	R3	R4	Formula
277143	5-(3-CF3-Ph)-2-Pyr	OH	H	H	C ₂₇ H ₂₈ F ₃ NO ₃
277144	6-OH-2-quinolinyl	H	H	H	C ₂₄ H ₂₇ NO ₃
277145	5-(3-Cl-Ph)-2-Pyr	H	H	H	C ₂₆ H ₂₈ ClNO ₂
277146	5-(2-F-Ph)-2-Pyr	H	H	H	C ₂₆ H ₂₈ FNO ₂
277147	5-Ph-2-Pyr	H	H	H	C ₂₆ H ₂₉ NO ₂
277148	5-[2,3-(F)2-Ph]-2-Pyr	H	H	H	C ₂₆ H ₂₇ F ₂ NO ₂
277149	5-(3-CF3-Ph)-2-Pyr	H	-O-		C ₂₇ H ₂₈ F ₃ NO ₃
277150	5-(3-CF3-Ph)-2-Pyr	H	OH	H	C ₂₇ H ₂₈ F ₃ NO ₃
277151	5-(3-CF3-Ph)-2-Pyr	H	H	OH	C ₂₇ H ₂₈ F ₃ NO ₃
277152	5-[3-(EtSO2NH)-Ph]-2-Pyr	H	H	H	C ₂₈ H ₃₄ N ₂ O ₄ S
277154	5-(3-Pyr)-2-Pyr	H	H	H	C ₂₅ H ₂₈ N ₂ O ₂



Compound	R1	R2	Formula
277153	H	H	C ₂₆ H ₂₀ F ₃ NO ₂
277155	F	F	C ₂₆ H ₁₈ F ₅ NO ₂

SOURCE – Schering-Plough.

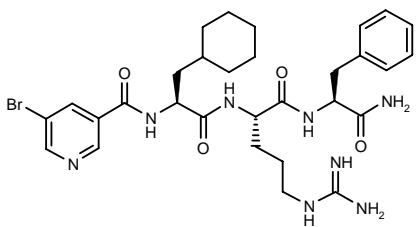
REFERENCES

1. Chackalamannil, S. et al. (Schering Corp.) *Thrombin receptor antagonists*. WO 9926943.

HEMOSTATICS

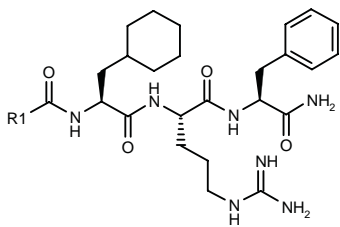
277390

N-(5-Bromopyridin-3-ylcarbonyl)-3-(cyclohexyl)-L-alanyl-L-arginyl-L-phenylalanylamide



C30 H41 Br N8 O4; Mol wt: 657.6099

ACTION – Thrombin receptor (PAR-1) ligand (IC₅₀ = 1.7 μM for inhibition of [³H]-S-(p-F-Phe)-Har-L-Har-KY-NH₂ binding in CHRF membrane preparations) with agonist activity in a platelet aggregation assay (EC₅₀ = 0.46 μM) and potency comparable to TRAP-6 (EC₅₀ = 0.28 μM). Other compounds from this series of heterocycle-peptide hybrids are:



Compound	R1	Formula
277064	5-NH2-1,2,4-triazol-3-yl	C ₂₇ H ₄₁ N ₁₁ O ₄
277392	4-oxo-1-benzopyran-2-yl	C ₃₄ H ₄₃ N ₇ O ₆

SOURCES – COR Therapeutics; R.W. Johnson.

REFERENCES

1. McComsey, D.F. et al. *Heterocycle-peptide hybrid compounds. Aminotriazole-containing agonists of the thrombin receptor (PAR-1)*. Bioorg Med Chem Lett 1999, 9(10): 1423.

MOROCTOCOG ALFA*

Prop INN

206991

(1-742)-(1637-1648)-Blood coagulation factor VIII (human reduced) complex with 1649-2332-blood coagulation factor VIII (human reduced)

r-Factor VIII SQ⁺
r-VIII SQ

ACTION – Recombinant, albumin-free formulation of coagulation factor VIII.

INDICATIONS – For the control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A.

PRESENTATION – Vials containing lyophilized powder for reconstitution with sodium chloride solution for injection, 250 IU.

PROPRIETARY NAME – ReFacto (GB).

SOURCES – Genetics Institute; Wyeth-Ayerst.

RECENT REFERENCES

1. Berntorp, E. et al. *Deletion of the B-domain in a recombinant factor VIII (r-VIII SQ) does not affect the main kinetic properties - Three pharmacokinetic studies in 36 patients with severe haemophilia A*. Thromb Haemost 1995, 73(6): Abst 437.

2. Berntorp, E. et al. *Prophylactic treatment with a B-domain-deleted recombinant factor VIII (r-VIII SQ) in previously treated patients with severe haemophilia A*. Thromb Haemost 1995, 73(6): Abst 427.

3. D'Oiron, R. et al. *Use of a modified chronometric method for the assay of a new recombinant factor VIII in severe haemophilia patients*. Haematologica 1999, 84(EHA-4): Abst PO-0914.

4. Fatouros, A. et al. *Recombinant factor VIII SQ: Stability in solution*. Pharm Res 1997, 14(11, Suppl.): Abst 1469.

5. Fijnvandraat, K. et al. *Quality of life of hemophilia A patients after introduction of a new recombinant F VIII concentrate (r-VIII SQ)*. Thromb Haemost 1995, 73(6): Abst 436.

6. Kessler, C.M. et al. *Safety and efficacy of a second generation, B-domain deleted recombinant factor VIII (r-VIII SQ) in previously treated patients (PTPs). A four year update*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2281.

7. Lusher, J.M. et al. *A four-year update of safety and efficacy of a second generation B-domain deleted factor VIII (r-VIII SQ) in previously untreated hemophilia A patients*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2282.

8. Österberg, T. and Fatouros, A. *Development of freeze-dried HSA-free formulation of a new recombinant factor VIII derivative, r-VIII SQ*. Thromb Haemost 1993, 69(6): Abst 1984.

9. Österberg, T. and Fatouros, A. *Physical stability of a freeze-dried HSA-free formulation for recombinant factor VIII SQ*. Pharm Res 1996, 13(9, Suppl.): Abst BIOTEC 2063.

10. Peters, M. et al. *A new B-domain deleted recombinant factor VIII concentrate (r-VIII SQ): Pharmacokinetics and tolerability of three doses*. Thromb Haemost 1995, 73(6): Abst 435.

11. Sandberg, H. et al. *Functional characteristics of a new recombinant factor VIII with a deleted B-domain, r-VIII SQ*. Thromb Haemost 1993, 69(6): Abst 2358.

12. Sandberg, H. et al. *Glycosylation of a B-domain-deleted recombinant factor VIII molecule (r-VIII SQ)*. Thromb Haemost 1995, 73(6): Abst 1202.

13. Smeds, A.-L. et al. *The purification process for recombinant factor VIII SQ*. Thromb Haemost 1995, 73(6): Abst 442.

14. *AHP launches ReFacto hemophilia A treatment in the U.K.* DailyDrugNews.com (Daily Essentials) 1999, June 21.

15. *BLA and MAA filed for recombinant factor VIII product for hemophilia A*. DailyDrugNews.com (Daily Essentials) 1998, May 22.

16. *European Commission approves novel albumin-free treatment for hemophilia A*. DailyDrugNews.com (Daily Essentials) 1999, April 19.

17. *New hemophilia treatment one step closer to market.* DailyDrugNews.com (Daily Essentials) 1998, Dec 15.

18. *Proposed international nonproprietary names: List No. 72.* WHO Drug Inf 1994, 8(4): 247.

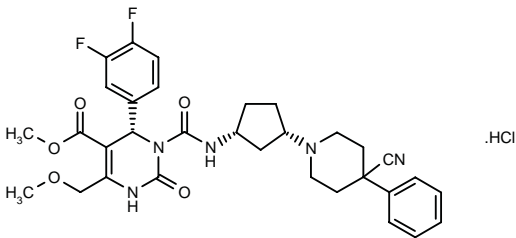
*Drug Data Report 1994, 016(06): 0554.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

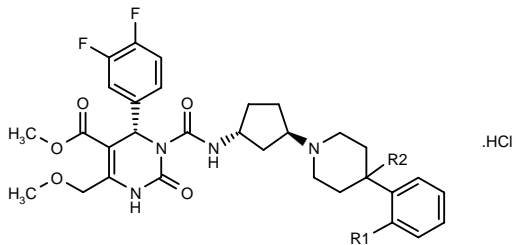
276980

3-[N-[3(*S*)-(4-Cyano-4-phenylpiperidin-1-yl)cyclopent-1(*R*)-yl]carbamoyl]-4(*S*)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride

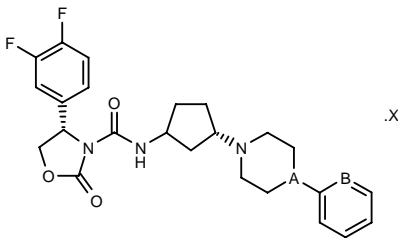


C32 H35 F2 N5 O5 . HCl; Mol wt: 644.1154

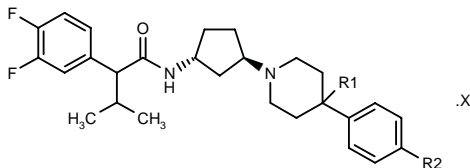
ACTION – Agent for the treatment of benign prostatic hyperplasia, a selective human α_{1a} -adrenoceptor antagonist with > 10-fold selectivity over α_{1b} - and α_{1d} -adrenoceptors and many other G-protein-coupled receptors. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
276981	H	CN	C ₃₂ H ₃₅ F ₂ N ₅ O ₅ .HCl
276983	CN	H	C ₃₂ H ₃₅ F ₂ N ₅ O ₅ .HCl



Compound	A	B	Isomer	X	Formula
276982	CH	N	R	2HCl	C ₂₅ H ₂₈ F ₂ N ₄ O ₃ .2HCl
276984	CH	C(CN)	S	HCl	C ₂₇ H ₂₈ F ₂ N ₄ O ₃ .HCl
276985	N	C(CN)	R	HCl	C ₂₆ H ₂₇ F ₂ N ₅ O ₃ .HCl



Compound	R1	R2	X	Formula
276990	CN	H		C ₂₈ H ₃₃ F ₂ N ₃ O
276991	H	F	HCl	C ₂₇ H ₃₃ F ₃ N ₂ O.HCl

SOURCE – Merck & Co.

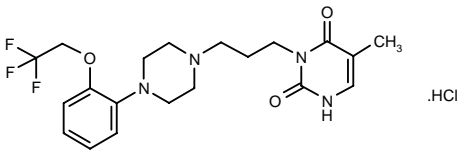
REFERENCES

1. Barrow, J. (Merck & Co., Inc.) α_{1a} -Adrenergic receptor antagonists. WO 9925345.

RS-100329*

245556

5-Methyl-3-[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride



C20 H25 F3 N4 O3 . HCl; Mol wt: 462.9030

ACTION – α_1 -Adrenoceptor antagonist with high selectivity for α_{1A} -adrenoceptors over α_{1B} - and α_{1D} -adrenoceptors, as demonstrated in binding experiments (pK_i = 9.6, 7.5 and 7.9, respectively, against [³H]-prazosin binding in CHO-K1 cells expressing cloned human α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors) and functional studies. Compound antagonized in a surmountable manner norepinephrine-induced contractions in human lower urinary tract and rabbit bladder neck tissues (pA_2 = 9.2 in both tissues) and was less potent in antagonizing norepinephrine-induced contractions in both human renal artery and rat aorta (pA_2 = 7.3 and 7.9, respectively). It is much more uroselective than prazosin, showing the same potency but higher selectivity for α_{1A} -adrenoceptors that mediate contractions of lower urinary tract tissue. Potentially useful for ameliorating urethral obstruction associated with benign prostatic hyperplasia (BPH).

17. *New hemophilia treatment one step closer to market.* DailyDrugNews.com (Daily Essentials) 1998, Dec 15.

18. *Proposed international nonproprietary names: List No. 72.* WHO Drug Inf 1994, 8(4): 247.

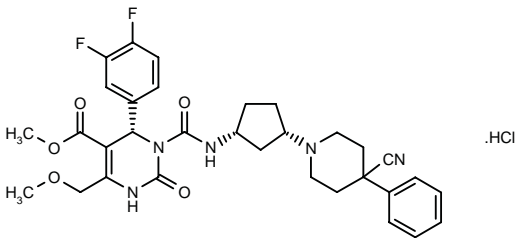
*Drug Data Report 1994, 016(06): 0554.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

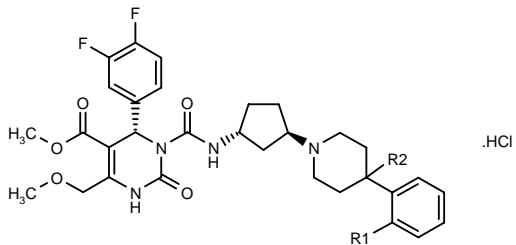
276980

3-[N-[3(S)-(4-Cyano-4-phenylpiperidin-1-yl)cyclopent-1(R)-yl]carbamoyl]-4(S)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride

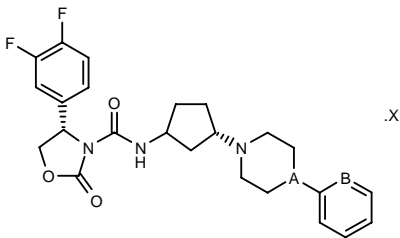


C32 H35 F2 N5 O5 . HCl; Mol wt: 644.1154

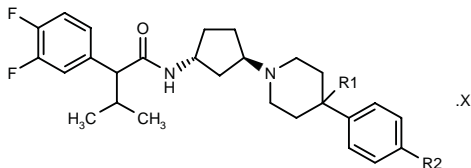
ACTION – Agent for the treatment of benign prostatic hyperplasia, a selective human α_{1a} -adrenoceptor antagonist with > 10-fold selectivity over α_{1b} - and α_{1d} -adrenoceptors and many other G-protein-coupled receptors. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
276981	H	CN	C ₃₂ H ₃₅ F ₂ N ₅ O ₅ .HCl
276983	CN	H	C ₃₂ H ₃₅ F ₂ N ₅ O ₅ .HCl



Compound	A	B	Isomer	X	Formula
276982	CH	N	R	2HCl	C ₂₅ H ₂₈ F ₂ N ₄ O ₃ .2HCl
276984	CH	C(CN)	S	HCl	C ₂₇ H ₂₈ F ₂ N ₄ O ₃ .HCl
276985	N	C(CN)	R	HCl	C ₂₆ H ₂₇ F ₂ N ₅ O ₃ .HCl



Compound	R1	R2	X	Formula
276990	CN	H		C ₂₈ H ₃₃ F ₂ N ₃ O
276991	H	F	HCl	C ₂₇ H ₃₃ F ₃ N ₂ O.HCl

SOURCE – Merck & Co.

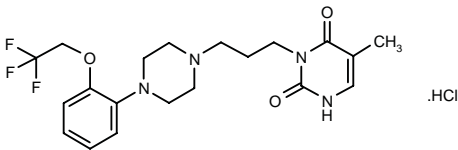
REFERENCES

1. Barrow, J. (Merck & Co., Inc.) α_{1a} -Adrenergic receptor antagonists. WO 9925345.

RS-100329*

245556

5-Methyl-3-[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]pyrimidine-2,4(1H,3H)-dione hydrochloride



C20 H25 F3 N4 O3 . HCl; Mol wt: 462.9030

ACTION – α_1 -Adrenoceptor antagonist with high selectivity for α_{1A} -adrenoceptors over α_{1B} - and α_{1D} -adrenoceptors, as demonstrated in binding experiments (pK_i = 9.6, 7.5 and 7.9, respectively, against [³H]-prazosin binding in CHO-K1 cells expressing cloned human α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors) and functional studies. Compound antagonized in a surmountable manner norepinephrine-induced contractions in human lower urinary tract and rabbit bladder neck tissues (pA_2 = 9.2 in both tissues) and was less potent in antagonizing norepinephrine-induced contractions in both human renal artery and rat aorta (pA_2 = 7.3 and 7.9, respectively). It is much more uroselective than prazosin, showing the same potency but higher selectivity for α_{1A} -adrenoceptors that mediate contractions of lower urinary tract tissue. Potentially useful for ameliorating urethral obstruction associated with benign prostatic hyperplasia (BPH).

SOURCE – Roche.

REFERENCES

1. Bantle, G.W. et al. (F. Hoffmann-La Roche AG) *Pyrimidinedione, pyrimidinetrione, triazinedione, tetrahydroquinazolinedione derivs. as α_1 -adrenergic receptor antagonists*. EP 748800, JP 97100269.

2. Kava, M.S. et al. *α_{1L} -Adrenoceptor mediation of smooth muscle contraction in rabbit bladder neck: A model for lower urinary tract tissues of man*. Br J Pharmacol 1998, 123(7): 1359.

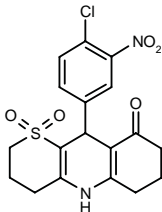
3. Williams, T.J. et al. *In vitro α_1 -adrenoceptor pharmacology of Ro 70-0004 and RS-100329, novel α_{1A} -adrenoceptor selective antagonists*. Br J Pharmacol 1999, 127(1): 252.

*Identified compound **245556** Drug Data Report 1997, 019(04): 0333.

TREATMENT OF URINARY INCONTINENCE

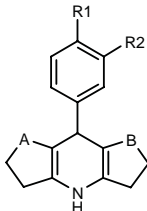
278029

10-(4-Chloro-3-nitrophenyl)-3,4,5,6,7,8,9,10-octahydro-2*H*-thiopyrano[3,2-*b*]quinoline-9-one 1,1-dioxide



C18 H17 Cl N2 O5 S; Mol wt: 408.8603

ACTION – Potassium channel opener ($pD_2 = 6.0$ and 5.8 in stimulated pig and human bladder strips, respectively) with EC_{50} values for membrane hyperpolarization in rat thoracic aorta A10 cells and guinea pig bladder cells of 0.39 and $0.43 \mu M$, respectively. It is thus able to reduce stimulated bladder contractions via opening of potassium channels and is expected to be particularly useful in the treatment of urinary incontinence. Its use in the treatment of asthma, epilepsy, hypertension, Raynaud’s syndrome, impotence, migraine, pain, eating disorders, functional bowel disorders, neurodegeneration and stroke is also claimed. Other exemplified 1,4-dihydropyridines include the following:



Compound	R1	R2	A	B	Isomer	Formula
278030	Cl	NO2	-CH2SO2-	-COCH2-		C ₁₇ H ₁₅ ClN ₂ O ₅ S
278031	F	Br	-CO-	-SO2CH2-		C ₁₇ H ₁₅ BrFNO ₃ S
278032	Cl	NO2	-SO2-	-CO-		C ₁₆ H ₁₃ ClN ₂ O ₅ S
278033	F	Cl	-CO-	-SO2-		C ₁₆ H ₁₃ ClFNO ₃ S
278034	F	Br	-CH2CO-	-SO2-	(+)-(R)	C ₁₇ H ₁₅ BrFNO ₃ S
278035	F	Br	-CO-	-SO2CH2-	(-)	C ₁₇ H ₁₅ BrFNO ₃ S

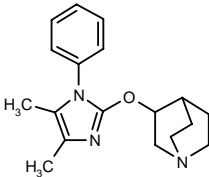
SOURCE – Abbott.

REFERENCES

1. Carroll, W.A. et al. (Abbott Laboratories Inc.) *Potassium channel openers*. WO 9931059.

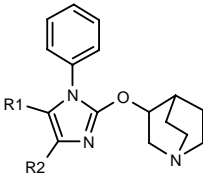
278091

3-(4,5-Dimethyl-1-phenyl-1*H*-imidazol-2-yloxy)quinuclidine



C18 H23 N3 O; Mol wt: 297.3997

ACTION – Muscarinic M_3 receptor antagonist with IC_{50} values in a binding assay of $1-350 \text{ nM}$ and pK_b values in a functional assay in carbachol-contracted rabbit detrusor preparations of $7-9.5$. Potentially useful in the treatment of irritable bowel syndrome, airways obstruction and bladder instability, especially urge urinary incontinence. Other specifically claimed imidazole derivatives are:



Compound	R1	R2	Formula
278092	-(CH2)4-		C ₂₀ H ₂₅ N ₃ O
278093	Et	Et	C ₂₀ H ₂₇ N ₃ O
278094	H	H	C ₁₆ H ₁₉ N ₃ O

SOURCE – Sanofi-Synthélabo.

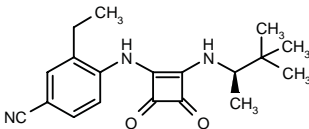
REFERENCES

1. Courtemanche, G. et al. (Sanofi SA) *Imidazol derivs. as muscarinic M3 receptor antagonists*. WO 9931097.

WAY-133537

277376

4-[3,4-Dioxo-2-[1(*R*),2,2-trimethylpropylamino]-1-cyclobuten-1-ylamino]-3-ethylbenzonitrile



C19 H23 N3 O2; Mol wt: 325.4097

ACTION – Potassium channel opener shown to antagonize KCl-induced contractions of isolated rat bladder detrusor strips ($IC_{50} = 0.09 \mu M$). *In vivo*, compound inhibited abnormal spontaneous contractions in a pathophysiological model of bladder instability in rats with hypertrophied bladder ($ED_{50} = 0.13 \text{ mg/kg p.o.}$), without affecting micturition pressure and at doses producing minimal hemodynamic changes. Potentially useful for the treatment of bladder instability in urge urinary incontinence.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Antane, M.M. et al. (American Home Products Corp.) *Diaminocyclobutene-3,4-diones*. EP 796243, JP 98509145, US 5464867, US 5530025, WO 9615103.
2. Butera, J.A. and Antane, S.A. (American Home Products Corp.) *Substd. N-heteroaryl and N-aryl-1,2-diaminocyclobutene-3,4-diones*. EP 729457, JP 97505296, US 5354763, WO 9514005.
3. Gast, M.J. and Koziol, T.R. (American Home Products Corp.) *Method of treating urinary incontinence*. WO 9811888.
4. Wojdan, A. et al. *Comparison of the potassium channel openers, WAY-133537, ZD6169, and celikalim on isolated bladder tissue and in vivo bladder instability in rat*. J Pharmacol Exp Ther 1999, 289(3): 1410.

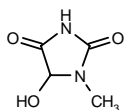
TREATMENT OF RENAL DISEASES

NZ-419*

112436

5-Hydroxy-1-methylhydantoin

5-Hydroxy-1-methylimidazolidine-2,4-dione



C4 H6 N2 O3; Mol wt: 130.1024

ACTION – Antioxidant found to inhibit the progression of adenine-induced chronic renal failure (CRF) in rats. Results from a clinical study in diabetic patients with CRF in which compound was administered orally at doses of 200 or 400 mg/day for up to 24 weeks indicated potential efficacy in the treatment of CRF.

SOURCE – Nippon Zoki.

REFERENCES

1. Ienaga, K. and Nakamura, K. (Nippon Zoki Pharmaceutical Co., Ltd.) *Hydantoin derivs. and pharmaceutical compns. containing them*. AU 8539172, EP 160618, ES 8609272, JP 86122275, US 4647574.
2. Mikami, H. and Ienaga, K. (Nippon Zoki Pharmaceutical Co., Ltd.) *Hydantoin or imidazolidinetrione derivs. for the prevention or treatment of renal failure*. EP 412940, JP 91072463, US 5084473.
3. Nakano, K. et al. *Effect of NZ-419 on diabetic chronic renal failure*. 15th Int Congr Nephrol (May 2-6, Buenos Aires) 1999, Abst 1534.

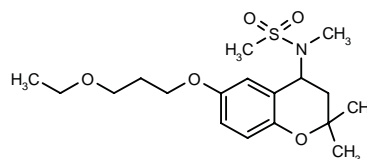
*Identified compound **112436** Drug Data Rep 1991, 013(07): 0582.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

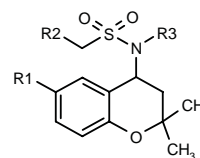
275001

N-[6-(3-Ethoxypropoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl]-*N*-methylmethanesulfonamide



C18 H29 N O5 S; Mol wt: 371.4951

ACTION – Gastric antisecretory agent that blocks cAMP-dependent K^+ channels ($IC_{50} = 0.32 \mu M$) and is also claimed for use as an antiarrhythmic agent. Other compounds from this series of sulfonamide-substituted chromanes include the following:



Compound	R1	R2	R3	Formula
275002	O(CH2)3OEt	H	Et	C ₁₉ H ₃₁ NO ₅ S
275003	OCH2CH2OEt	H	Et	C ₁₈ H ₂₉ NO ₅ S
275004	2-thienyl	Me	Me	C ₁₈ H ₂₅ NO ₃ S ₂

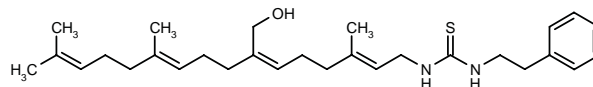
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulfonamid-substd. chromane derivs. (K⁺ channel-blocker), process for their preparation, their use as drugs and pharmaceutical compns. containing them*. EP 906911, JP 99158171.

277031

N-[7-(Hydroxymethyl)-3,11,15-trimethylhexadeca-2(*E*),6(*Z*),10(*E*),14-tetraenyl]-*N'*-(2-phenylethyl)thiourea



C29 H44 N2 O S; Mol wt: 468.7456

ACTION – Antibacterial agent active against *Helicobacter pylori* with MICs < 0.10 $\mu g/ml$ against strains NCTC 11637, CPY 2052 and No. 7 and potency comparable to amoxicillin. *In vivo*, compound (100 mg/kg/day p.o. for 10 days) showed antiulcer activity in *H. pylori*-infected mice with acetic acid-induced gastric ulcers.

ACTION – Potassium channel opener shown to antagonize KCl-induced contractions of isolated rat bladder detrusor strips ($IC_{50} = 0.09 \mu M$). *In vivo*, compound inhibited abnormal spontaneous contractions in a pathophysiological model of bladder instability in rats with hypertrophied bladder ($ED_{50} = 0.13 \text{ mg/kg p.o.}$), without affecting micturition pressure and at doses producing minimal hemodynamic changes. Potentially useful for the treatment of bladder instability in urge urinary incontinence.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Antane, M.M. et al. (American Home Products Corp.) *Diaminocyclobutene-3,4-diones*. EP 796243, JP 98509145, US 5464867, US 5530025, WO 9615103.
2. Butera, J.A. and Antane, S.A. (American Home Products Corp.) *Substd. N-heteroaryl and N-aryl-1,2-diaminocyclobutene-3,4-diones*. EP 729457, JP 97505296, US 5354763, WO 9514005.
3. Gast, M.J. and Koziol, T.R. (American Home Products Corp.) *Method of treating urinary incontinence*. WO 9811888.
4. Wojdan, A. et al. *Comparison of the potassium channel openers, WAY-133537, ZD6169, and celikalim on isolated bladder tissue and in vivo bladder instability in rat*. J Pharmacol Exp Ther 1999, 289(3): 1410.

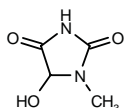
TREATMENT OF RENAL DISEASES

NZ-419*

112436

5-Hydroxy-1-methylhydantoin

5-Hydroxy-1-methylimidazolidine-2,4-dione



C4 H6 N2 O3; Mol wt: 130.1024

ACTION – Antioxidant found to inhibit the progression of adenine-induced chronic renal failure (CRF) in rats. Results from a clinical study in diabetic patients with CRF in which compound was administered orally at doses of 200 or 400 mg/day for up to 24 weeks indicated potential efficacy in the treatment of CRF.

SOURCE – Nippon Zoki.

REFERENCES

1. Ienaga, K. and Nakamura, K. (Nippon Zoki Pharmaceutical Co., Ltd.) *Hydantoin derivs. and pharmaceutical compns. containing them*. AU 8539172, EP 160618, ES 8609272, JP 86122275, US 4647574.
2. Mikami, H. and Ienaga, K. (Nippon Zoki Pharmaceutical Co., Ltd.) *Hydantoin or imidazolidinetrione derivs. for the prevention or treatment of renal failure*. EP 412940, JP 91072463, US 5084473.
3. Nakano, K. et al. *Effect of NZ-419 on diabetic chronic renal failure*. 15th Int Congr Nephrol (May 2-6, Buenos Aires) 1999, Abst 1534.

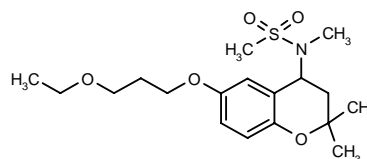
*Identified compound **112436** Drug Data Rep 1991, 013(07): 0582.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

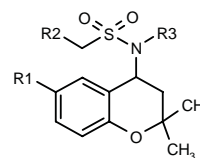
275001

N-[6-(3-Ethoxypropoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl]-*N*-methylmethanesulfonamide



C18 H29 N O5 S; Mol wt: 371.4951

ACTION – Gastric antisecretory agent that blocks cAMP-dependent K^+ channels ($IC_{50} = 0.32 \mu M$) and is also claimed for use as an antiarrhythmic agent. Other compounds from this series of sulfonamide-substituted chromanes include the following:



Compound	R1	R2	R3	Formula
275002	O(CH2)3OEt	H	Et	C ₁₉ H ₃₁ NO ₅ S
275003	OCH2CH2OEt	H	Et	C ₁₈ H ₂₉ NO ₅ S
275004	2-thienyl	Me	Me	C ₁₈ H ₂₅ NO ₃ S ₂

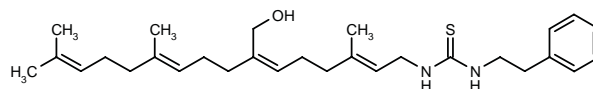
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulfonamid-substd. chromane derivs. (K⁺ channel-blocker), process for their preparation, their use as drugs and pharmaceutical compns. containing them*. EP 906911, JP 99158171.

277031

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C29 H44 N2 O S; Mol wt: 468.7456

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SOURCE – Sankyo.

REFERENCES

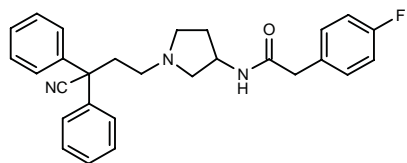
1. Akiyama, T. et al. (Sankyo Co., Ltd.) *Thiourea derivs. of plaunotols*. JP 97165368.

2. Kogen, H. et al. *A highly stereoselective synthesis of plaunotol and its thiourea derivatives as potent antibacterial agents against Helicobacter pylori*. Bioorg Med Chem Lett 1999, 9(10): 1347.

AGENTS FOR IRRITABLE BOWEL SYNDROME

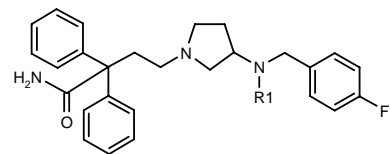
276590

N-[1-(3-Cyano-3,3-diphenylpropyl)pyrrolidin-3-yl]-2-(4-fluorophenyl)acetamide

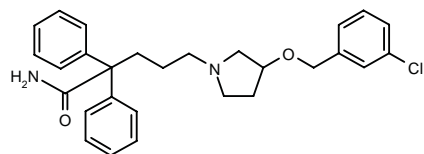


C28 H28 F N3 O; Mol wt: 441.5472

ACTION – Muscarinic receptor antagonist for the treatment of irritable bowel syndrome. A representative compound from a series of N-substituted cyclic amine derivatives, wherein the following are also included:



Compound	R1	Formula
276592	H	C27H30FN3O
276594	Ac	C29H32FN3O2



276591: C28 H31 Cl N2 O2

SOURCE – Kyorin.

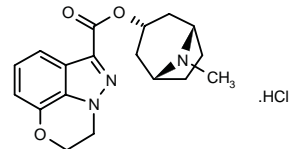
REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Novel N-substd. cyclic amine derivs. and their preparation method*. JP 99100366.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

276043

2,3-Dihydropyrazolo[1,5,4-de]-1,4-benzoxazine-6-carboxylic acid *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester hydrochloride



C18 H21 N3 O3 . HCl; Mol wt: 363.8428

ACTION – Agent for the treatment of functional disorders of the gastrointestinal tract such as intestinal motor and secretory disorders, irritable bowel syndrome, diarrhea, reflux esophagus, nausea and vomiting, among others, a 5-HT₃ and 5-HT₄ receptor antagonist (IC₅₀ = 2.5 and 5.2 nM, respectively, in conventional receptor binding assays); it had a pK_b value of 8.0 for 5-HT₄ receptor antagonism in a functional assay. A representative compound from a series of specifically claimed benzoxazine derivatives.

SOURCE – Sanofi-Synthélabo.

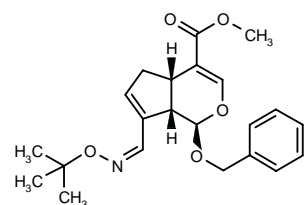
REFERENCES

1. Even, L. et al. (Synthélabo) *Benzoxazine derivs., preparation and application in therapy*. WO 9920633.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

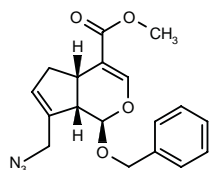
276702

(1*R*,4*aS*,7*aS*)-1-Benzyloxy-7-(*tert*-butoxyiminomethyl)-1,4*a*,5,7*a*-tetrahydrocyclopenta[*c*]pyran-4-carboxylic acid methyl ester

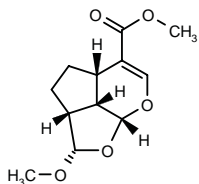


C22 H27 N O5; Mol wt: 385.4573

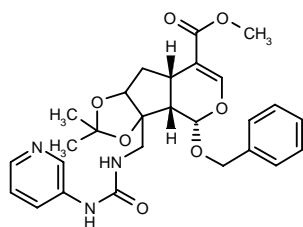
ACTION – Hepatoprotective and antihepatitis agent with an ED₅₀ value of 30 μM when assessed *in vitro* for inhibition of HBV replication in 2.2.15 cells (ED₅₀ ddC = 15 μM); it showed low cytotoxic potential in uninfected cells (IC₅₀ = 120 μM; IC₅₀ ddC > 30 μM). *In vivo*, it exhibited protective effects against hepatotoxicity elicited by CCl₄ in rats, with 64% inhibition of the increase in ALT at a dose of 100 mg/kg/day p.o. x 4 days. No mortality was observed following administration of up to 2000 mg/kg p.o. to mice. Within this series of genipin derivatives, the following are also included:



276703: C18 H19 N3 O4



276704: C12 H16 O5



276706: C27 H31 N3 O7

SOURCE – Choongwae.

REFERENCES

1. Moon, S.H. et al. (Choongwae Pharma Corp.) *Novel genipin deriv. having liver protection activity*. WO 9923090.

ISIS-14803¹⁻³

275588

20-Mer phosphorothioate antisense oligodeoxynucleotide whose sequence is:

5'-GTGCmTCmATGGTGcMACm-GGTCmT-3' where Cm represents 5-methylcytidine

ACTION – Antiviral agent, a phosphorothioate antisense oligodeoxynucleotide with a sequence complementary to the sequence of the highly conserved region surrounding the hepatitis C virus (HCV) translation initiation codon and specific inhibitory activity against HCV; it is a 5-methylcytidine version of **ISIS-6547**. Compound (2-20 mg/kg s.c.) inhibited HCV gene expression (luciferase activity) in the liver of recombinant HCV–vaccinia virus-infected mice.

20-mer phosphodiesterase antisense oligodeoxynucleotide whose sequence is:

5'-GTGCTCATGGTGACGGTCT-3'

ISIS-6547 [277049]³

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Anderson, K.P. *Antisense oligonucleotides: Novel therapeutics for viral disease*. J Antimicrob Chemother 1999, 44(Suppl. A): Abst 34-68.

2. Hanecak, R. et al. *Second oligonucleotide inhibition of hepatitis C virus gene expression in transfected hepatocytes*. J Virol 1996, 70(8): 5203.

3. Zhang, H. et al. *Antisense oligonucleotide inhibition of hepatitis C virus (HCV) gene expression in livers of mice infected with an HCV-vaccinia virus recombinant*. Antimicrob Agents Chemother 1999, 43(2): 347.

SHANVAC-B

274208

Recombinant DNA hepatitis B vaccine containing hepatitis B surface antigen (HBsAg; subtype adw2), produced in genetically engineered yeast cells

ACTION – Recombinant hepatitis B vaccine providing geometric mean titers in mice higher than the reference plasma-derived vaccine or the recombinant vaccine *Engerix-B*. In adult human volunteers negative for hepatitis B markers, vaccine (administered as 3 doses of 20 µg at 1-month intervals) afforded complete seroprotection up to 1 month after the third dose, giving effective antihepatitis B titers of 11, 266 and 2246 mIU/ml, respectively, after the first, second and third doses and being devoid of side effects.

SOURCE – Shantha Biotechnics.

REFERENCES

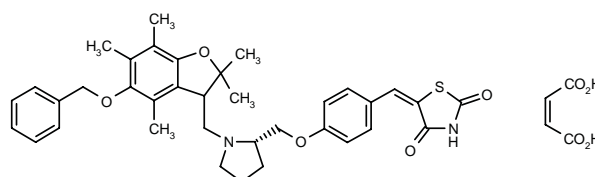
1. Abraham, P. et al. *Evaluation of a new recombinant DNA hepatitis B vaccine (Shanvac-B)*. Vaccine 1999, 17(9-10): 1125.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

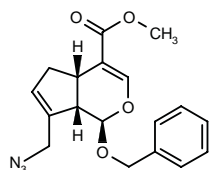
275299

(E)-5-[4-[1-(5-Benzyloxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-3-ylmethyl)pyrrolidin-2(S)-yl]-methoxy]benzylidene]thiazolidine-2,4-dione maleate

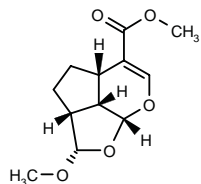


C36 H40 N2 O5 S . C4 H4 O4; Mol wt: 728.8586

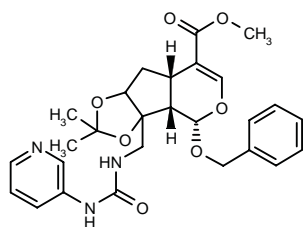
ACTION – Hypoglycemic and hypolipidemic agent shown to decrease both blood glucose and triglyceride levels (45 and 42%, respectively, at 30 mg/kg/day p.o. for 6 days) in *db/db* mice; it was more potent than troglitazone (26 and 50% decrease, respectively, at 200 mg/kg/day). Compound showed a good oral pharmacokinetic profile, with slow absorption ($t_{\max} = 5$ h) and high C_{\max} (4.3 µg/ml). It does not induce significant transactivation of either PPARα or PPARγ receptors, suggesting that its pharmacological activity may be mediated through some other mechanism.



276703: C18 H19 N3 O4



276704: C12 H16 O5



276706: C27 H31 N3 O7

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SOURCE – Shantha Biotechnics.

REFERENCES

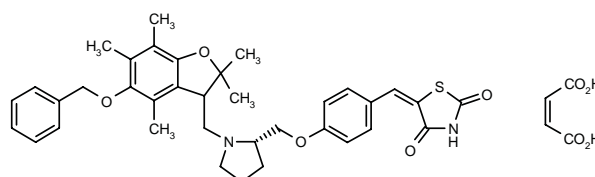
1. Abraham, P. et al. *Evaluation of a new recombinant DNA hepatitis B vaccine (Shanvac-B)*. Vaccine 1999, 17(9-10): 1125.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

275299

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SOURCE – Dr. Reddy’s Research Foundation, Hyderabad (IN).

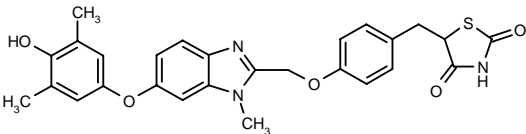
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1. Lohray, V.B. et al. (Dr. Reddy’s Research Foundation) *Heterocyclic cpds. having antidiabetic, hypolipidaemic, antihypertensive properties, process for their preparation and pharmaceutical compsns. containing them.* US 5889032.

2. Reddy, K.A. et al. *Novel antidiabetic and hypolipidemic agents. 3. Benzofuran-containing thiazolidinediones.* J Med Chem 1999, 42(11): 1927.

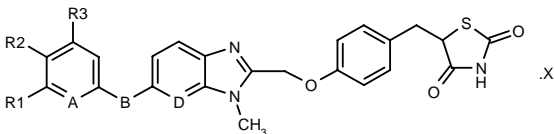
276725

5-[4-[6-(4-Hydroxy-3,5-dimethylphenoxy)-1-methyl-1*H*-benzimidazol-2-ylmethoxy]benzyl]thiazolidine-2,4-dione



C27 H25 N3 O5 S; Mol wt: 503.5765

ACTION – Hypoglycemic agent with antioxidant and 5-lipoxygenase-inhibitory effects. It reduced blood glucose levels by 67.5% in diabetic KK mice when given in the diet, and it had IC₅₀ values of 0.83 and 0.20 µg/ml, respectively, for inhibition of lipid peroxidation in rat hepatic microsomes and of 5-lipoxygenase in guinea pig polymorphonuclear leukocytes. Other substituted fused heterocyclic compounds include the following:



Compound	R1	R2	R3	A	B	D	X	Formula
276728	Me	OH	Me	C(Me)	O	CH		C ₂₈ H ₂₇ N ₃ O ₅ S
276729	Me	OH	Me	C(Me)	O	N	HCl	C ₂₇ H ₂₆ N ₄ O ₅ S.ClH
276731	t-Bu	OH	t-Bu	CH	S	CH	HCl	C ₃₃ H ₃₇ N ₃ O ₄ S ₂ .HCl
276733	H	H	H	N	S	CH	2HCl	C ₂₄ H ₂₀ N ₄ O ₃ S ₂ .2HCl
276735	H	SMe	H	CH	O	CH	HCl	C ₂₆ H ₂₃ N ₃ O ₄ S ₂ .HCl

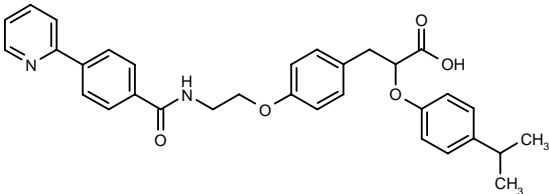
SOURCE – Sankyo.

REFERENCES

1. Fujita, T. et al. (Sankyo Co., Ltd.) *Substd. fused heterocyclic cpds.* WO 9918081.

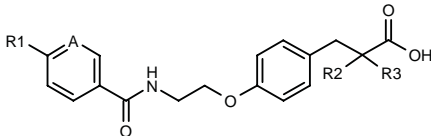
276741

2-(4-Isopropylphenoxy)-3-[4-[2-[4-(2-pyridinyl)benz-amido]ethoxy]phenyl]propionic acid isomer A



C32 H32 N2 O5; Mol wt: 524.6138

ACTION – Hypoglycemic agent for use in the treatment or prophylaxis of diabetes, hyperlipidemia, arteriosclerosis, hypertension and the like. Compound reduced blood glucose levels in KK mice by 73% at a dose of about 10 mg/kg/day in the diet for 3 days. Other representative compounds from this series of aminocarboxylic acid derivatives are:



Compound	R1	R2	R3	A	Formula
276742	2-Pyr	4-i-Pr-PhO	H	CH	C ₃₂ H ₃₂ N ₂ O ₅
276743	2-Pyr	OPh	Me	CH	C ₃₀ H ₂₈ N ₂ O ₅
276744	2-Pyr	4-i-Pr-PhO	Me	CH	C ₃₃ H ₃₄ N ₂ O ₅
276745	2-Pyr	Pr	H	CH	C ₂₆ H ₂₈ N ₂ O ₄
276746	Ph	4-i-Pr-PhO	H	N	C ₃₂ H ₃₂ N ₂ O ₅
276747	5-NMe2-2-Pyr	4-i-Pr-PhO	H	CH	C ₃₄ H ₃₇ N ₃ O ₅
276748	2-Pyr	4-t-Bu-PhO	H	CH	C ₃₃ H ₃₄ N ₂ O ₅
276749	2-Pyr	4-Cl-PhO	H	CH	C ₂₉ H ₂₅ ClN ₂ O ₅

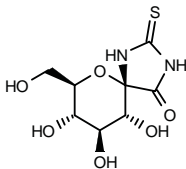
SOURCE – Sankyo.

REFERENCES

1. Yanagisawa, H. et al. (Sankyo Co., Ltd.) *Amidocarboxylic acid derivs.* WO 9918066.

277062⁵

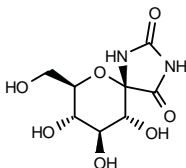
(5*S*,7*R*,8*S*,9*S*,10*R*)-8,9,10-Trihydroxy-7-(hydroxymethyl)-2-thioxo-6-oxa-1,3-diazaspiro[4.5]decan-4-one



C8 H12 N2 O6 S; Mol wt: 264.2568

Amorphous solid, [α]_D¹⁹ +19° (c 2.34, MeOH).

ACTION – Potential antidiabetic agent, an inhibitor of liver and muscle glycogen phosphorylases *a* and *b* (K_i = 29.8 and 7 µM for rat liver phosphorylase *a* and *b*, respectively, and 10.9 and 5.1 µM for rabbit muscle phosphorylase *a* and *b*, respectively). Also potentially useful as a pharmacological tool for elucidating the role of these enzymes in the pathophysiology of type II diabetes. Another related compound is:



277478: C8 H12 N2 O7¹⁻⁸

SOURCE – Lajos Kossuth University, Debrecen (HU).

REFERENCES

1. Bichard, C.J.F. et al. *Potent inhibition of glycogen phosphorylase by a spirohydantoin of glucopyranose: First pyranose analogs of hydanocidin*. Tetrahedron Lett 1995, 36(12): 2145.

2. De la Fuente, C. et al. *Glucopyranose spirohydantoins. Specific inhibitors of glycogen phosphorylase*. Synlett 1997, (5): 485.

3. Gregoriou, M. et al. *The structure of a glycogen phosphorylase glucopyranose spirohydantoin complex at 1.8 Angstrom resolution and 100 K: The role of the water structure and its contribution to binding*. Protein Sci 1998, 7(4): 915.

4. Krulle, T.M. et al. *Stereospecific synthesis of spirohydantoins of beta-glucopyranose. Inhibitors of glycogen phosphorylase*. Synlett 1997, (2): 211.

5. Osz, E. et al. *Efficient inhibition of muscle and liver glycogen phosphorylases by a new glucopyranosylidene-spiro-thiohydantoin*. Bioorg Med Chem Lett 1999, 9(10): 1385.

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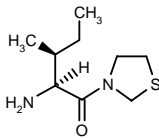
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277261

2(S)-Amino-3(S)-methyl-1-(3-thiazolidinyl)pentan-1-one

3-(L-Isoleucyl)thiazolidine

3-[2(S)-Amino-3(S)-methylpentanoyl]thiazolidine



C9 H18 N2 O S; Mol wt: 202.3202

ACTION – Dipeptidyl peptidase IV (DPP-IV) inhibitor ($K_i = 0.126 \mu\text{M}$ against enzyme from pig kidney) with comparable potency against human prolyl endopeptidase ($K_i = 0.183 \mu\text{M}$) and good selectivity over human placenta DPP-II ($K_i = 7.06 \mu\text{M}$) and bacterial aminopeptidase P (APP; $K_i = 2.14 \text{ mM}$). In lean and obese Zucker rats, compound (20 $\mu\text{mol}/300 \text{ g}$ body weight p.o.) significantly decreased (65%) circulating DPP-IV levels at 30 min, with the consequent enhancement of insulin secretion, particularly in obese animals (150% vs. 27% in lean rats). Compound improved glucose tolerance in both phenotypes and restored glucose tolerance to near-normal levels in obese animals. Potentially useful for the treatment of type II diabetes and other disorders involving glucose intolerance.

SOURCES – Hans Knöll Institute for Natural Products Research, Halle (DE); Martin Luther Universität, Halle (DE).

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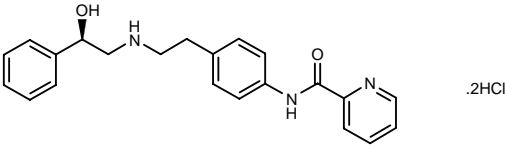
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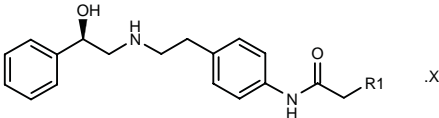
277323

N-[4-[2-[2(R)-Hydroxy-2-phenylethylamino]ethyl]-phenyl]pyridine-2-carboxamide dihydrochloride



C22 H23 N3 O2 . 2HCl; Mol wt: 434.3645

ACTION – Selective β_3 -adrenoceptor agonist that reduces blood sugar levels in diabetic, obese KK mice and normal rats and accelerates insulin secretion in normal rats, making it potentially useful as an antidiabetic, antiobesity and/or antihyperlipidemic agent. Other exemplified compounds include the following:



Compound	R1	X	Formula
277324	1-(4-Cl-PhCH2)-2-imidazolyl	2HCl	C ₂₈ H ₂₉ ClN ₄ O ₂ ·2HCl
277325	1-[3,4-(Cl)2-PhCH2]-5-tetrazolyl	HCl	C ₂₆ H ₂₆ Cl ₂ N ₆ O ₂ ·HCl
277326	2-NH2-4-thiazolyl	2HCl	C ₂₁ H ₂₄ N ₄ O ₂ ·2HCl
277327	1-(PhCH2)-1,2,4-triazol-5-yl	HCl	C ₂₇ H ₁₉ N ₅ O ₂ ·HCl
277328	6-NH2-2-Pyr	2HCl	C ₂₃ H ₂₆ N ₄ O ₂ ·2HCl
277329	2-Pyr	HCl	C ₂₃ H ₂₅ N ₃ O ₂ ·HCl
277330	2-pyrazinyl	HCl	C ₂₂ H ₂₄ N ₄ O ₂ ·HCl
277331	2-pyrimidinyl	HCl	C ₂₂ H ₂₃ N ₄ O ₂ ·HCl

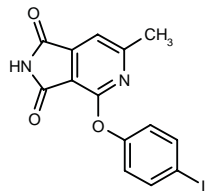
SOURCE – Yamanouchi.

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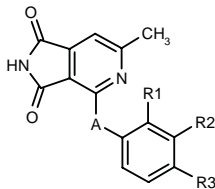
278095

4-(4-Iodophenoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo-[3,4-*c*]pyridine-1,3-dione



C14 H9 I N2 O3; Mol wt: 380.1361

ACTION – Hypoglycemic agent particularly useful for the treatment and/or prevention of non-insulin-dependent diabetes mellitus. It is thought to reduce blood glucose mainly by stimulating glucose uptake into muscle and fat cells. The compound reduces blood glucose levels without affecting circulating insulin levels and is suitable for both acute and chronic therapy. Other exemplified pyridine and pyrimidine derivatives include the following:



Compound	R1	R2	R3	A	Formula
278096	H	H	H	O	C ₁₄ H ₁₀ N ₂ O ₃
278097	H	Cl	Cl	O	C ₁₄ H ₈ Cl ₂ N ₂ O ₃
278098	H	H	Me	O	C ₁₅ H ₁₂ N ₂ O ₃
278099	H	H	F	S	C ₁₄ H ₉ FN ₂ O ₂ S
278100	NH2	H	H	S	C ₁₄ H ₁₁ N ₃ O ₂ S

SOURCE – Novo Nordisk.

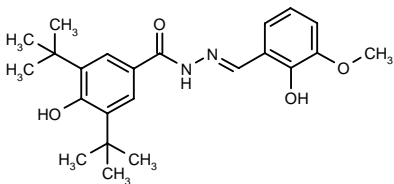
REFERENCES

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TREATMENT OF DIABETIC COMPLICATIONS

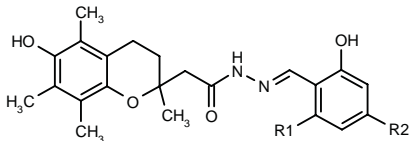
276653

3,5-Di-*tert*-butyl-4-hydroxy-*N'*-(2-hydroxy-3-methoxybenzylidene)benzohydrazide

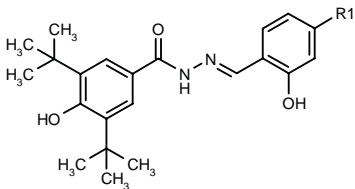


C23 H30 N2 O4; Mol wt: 398.5000

ACTION – Agent for the treatment of diabetic complications, an inhibitor of the formation of advanced glycosylation endproducts (AGEs; IC₅₀ = 0.63 μM) also shown to inhibit lipid peroxidation *in vitro* in rat renal homogenates. *In vivo*, the compound reduced urinary albumin excretion in streptozotocin-diabetic rats at a dose of 100 mg/kg/day p.o. x 3 weeks. No mortality was observed following administration of up to 2000 mg/kg p.o. to rats. A compound within a series of acylhydrazone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
276654	OMe	OMe	C ₂₄ H ₃₀ N ₂ O ₆
276657	H	i-PrO	C ₂₅ H ₃₂ N ₂ O ₅



Compound	R1	Formula
276655	i-PrO	C ₂₅ H ₃₄ N ₂ O ₄
276656	N(Me)2	C ₂₄ H ₃₃ N ₃ O ₃

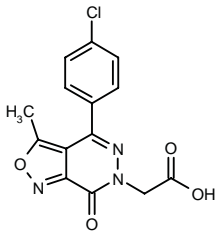
SOURCE – Nisshin Flour Milling.

REFERENCES

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277075

2-[4-(4-Chlorophenyl)-3-methyl-7-oxoisoxazolo[3,4-*d*]-pyridazin-6-yl]acetic acid



C14 H10 Cl N3 O4; Mol wt: 319.7030

ACTION – Aldose reductase inhibitor (IC₅₀ = 3.72 μM) with activity comparable to sorbinil (IC₅₀ = 3.04 μM). Potentially useful for the treatment of diabetic complications.

SOURCES – Istituto Chimico Farmaceutico e Tossicologico, Milano (IT); Università degli Studi di Firenze, Firenze (IT); Università degli Studi di Modena, Modena (IT).

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1. Constantino, L. et al. *Isoxazolo-[3,4-d]-pyridazin-7-(6H)-one as a potential substrate for new aldose reductase inhibitors.* J Med Chem 1999, 42(11): 1894.

huA717-ScFv

276936

Humanized A717 immunoglobulin single-chain Fv

ACTION – Genetically engineered humanized single-chain immunoglobulin with potential for the treatment of complications of diabetes caused by excess circulating glycated albumin by virtue of its ability to selectively react with human glycated albumin, as demonstrated in a binding assay.

SOURCE – Exocell.

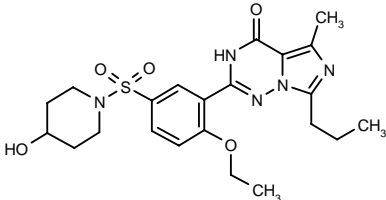
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TREATMENT OF MALE SEXUAL DYSFUNCTION

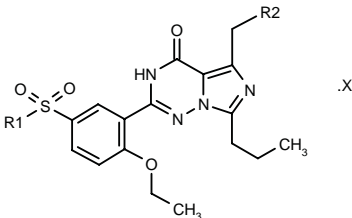
276895

2-[2-Ethoxy-5-(4-hydroxypiperidin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one



C22 H29 N5 O5 S; Mol wt: 475.5671

ACTION – An inhibitor of cGMP-phosphodiesterases such as PDE1 (IC₅₀ = 100 nM) and PDE5 (IC₅₀ = 1 nM) with potential in the treatment of cardiovascular and cerebrovascular disorders, as well as disorders of the urogenital system, and especially for treating erectile dysfunction. Other specifically claimed compounds within this series of 2-phenyl substituted imidazotriazinone derivatives include the following:



Compound	R1	R2	X	Formula
276896	4-Me-1-Piz	H		C ₂₂ H ₃₀ N ₆ O ₄ S
276898	4-cyclopentyl-1-Piz	H		C ₂₆ H ₃₆ N ₆ O ₄ S
276899	4-(CH ₂ CH ₂ OH)-1-Piz	H		C ₂₃ H ₃₂ N ₆ O ₅ S
276900	4-Et-1-Piz	H		C ₂₃ H ₃₂ N ₆ O ₄ S
276901	4-Me-1-Piz	Me		C ₂₃ H ₃₂ N ₆ O ₄ S
276902	4-morpholinyl	H		C ₂₁ H ₂₇ N ₅ O ₅ S
276903	4-Et-1-Piz	H	2HCl	C ₂₃ H ₃₃ N ₆ O ₄ S .2HCl

Compound	R1	R2	X	Formula
276904	N(Et)2	H		C ₂₁ H ₂₉ N ₅ O ₄ S
276905	N(Pr)CH ₂ CH ₂ OH	H		C ₂₂ H ₃₁ N ₅ O ₅ S
276906	4-Et-1-Piz	H	HCl.3H ₂ O	C ₂₃ H ₃₃ N ₆ O ₄ S .HCl.3H ₂ O

SOURCE – Bayer.

REFERENCES

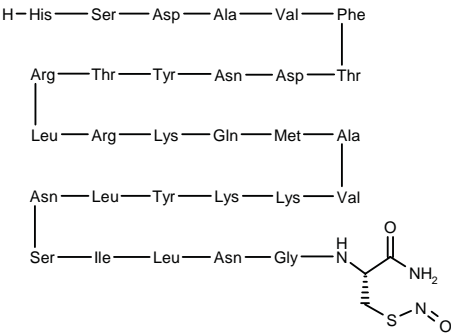
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VIPGC-NO*

243767

Histidyl-seryl-aspartyl-alanyl-valyl-phenylalanyl-threonyl-aspartyl-asparaginyl-tyrosyl-threonyl-arginyl-leucyl-arginyl-lysyl-glutamyl-methionyl-alanyl-valyl-lysyl-lysyl-tyrosyl-leucyl-asparaginyl-seryl-isoleucyl-leucyl-asparaginyl-glycyl-(S-nitroso)cysteinamide

28a-Glycine-28b-(S-nitroso-L-cysteinamide)-vasoactive intestinal octacosapeptide (swine)



C152 H245 N47 O45 S2; Mol wt: 3515.0230

ACTION – A synthetic nitroso derivative of vasoactive intestinal peptide (VIP) that relaxes vascular and nonvascular smooth muscle via the cGMP and cAMP pathway. In isolated phenylephrine-precontracted rabbit aorta, compound (1 μM) induced complete vasorelaxation and a significant increase in cGMP, whereas VIP (1 μM) only produced 19% relaxation and at least a 3-fold lower cGMP increase; in tracheal rings, vasorelaxation was associated with a marked increase in cAMP levels. It relaxed methacholine-precontracted guinea pig tracheal rings with an EC₅₀ of 32 ± 6 nM (EC₅₀ VIP = 74 ± 5 nM), it inhibited spontaneous (91% at 1 μM) and acetylcholine-induced contractions (90% at 1 μM) in rabbit sphincter of Oddi, and it also relaxed spontaneous contractions in rat gastric fundus strips. This compound thus appears to maintain the intrinsic activity of VIP and to acquire NO-like vasoactivity. Claimed in patent literature to be useful in the treatment or diagnosis of impotence.

SOURCES – Boston University, Boston, MA (US); Brigham & Women’s Hospital, Boston, MA (US); La Jolla Pharmaceutical.

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*Identified compound **243767** Drug Data Report 1997, 019(02): 0144.

AGENTS FOR FEMALE INFERTILITY

CETRORELIX*

Rec INN

148387

Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-seryl-tyrosyl-D-citrullyl-leucyl-arginyl-prolyl-D-alaninamide

Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-seryl-tyrosyl-D-N⁵-carbamoylornithyl-leucyl-arginyl-prolyl-D-alaninamide

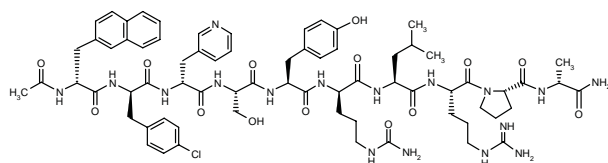
D-20453 (trifluoroacetate)

D-20761 (acetate)

NS-75A

SB-075⁺

SB-75



C70 H92 Cl N17 O14; Mol wt: 1431.0550

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist that binds to pituitary LHRH receptors and effectively inhibits the release of LH from the pituitary gland.

INDICATIONS – Prevention of premature ovulation in women undergoing controlled ovarian stimulation.

PRESENTATION – Vials, lyophilized powder for s.c. injection, 0.25 and 3.0 mg.

PROPRIETARY NAME – *Cetrotide* (DE, GB).

SOURCES – Asta Medica; comarketed by Ares-Serono.

RECENT REFERENCES

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2. Bajusz, S. et al. *Highly potent antagonists of luteinizing hormone-releasing hormone free of edematogenic effects.* Proc Natl Acad Sci USA 1988, 85: 1637.

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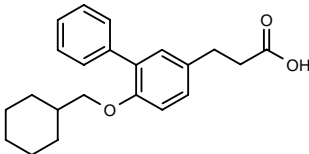
MONOGRAPH – Reissmann, T. et al. *Cetrorelix*. Drugs Fut 1994, 019(03): 0228.

*Drug Data Report 1989, 011(10): 0838.

DERMATOLOGIC DRUGS

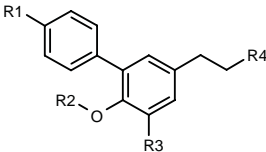
277251

3-[6-(Cyclohexylmethoxy)biphenyl-3-yl]propionic acid



C22 H26 O3; Mol wt: 338.4444

ACTION – Cytokine and IgE antibody production inhibitor; it produced 62.0% inhibition of antigen-induced IgE antibody production in the passive cutaneous anaphylaxis reaction in mice following oral dosing with 10 mg/kg/day for 5 days, and it also inhibited the production of IL-4 and IL-5 in spleen cells from sensitized mice by at least 50% at concentrations of 1-10 µg. Significant inhibition of the immediate allergic paw edema response was also observed in mice administered doses of 3-100 mg/kg/day p.o. for 5 days. It is expected to be useful in the treatment of allergic disorders. Other exemplified biphenyl-5-alkanoic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
277252	H	cyclopentyl	H	CO2H	C ₂₀ H ₂₂ O ₃
277253	H	cyclohexyl-CH2	NHCONH2	CO2H	C ₂₃ H ₂₈ N ₂ O ₄
277254	OH	cyclohexyl-CH2	H	CO2H	C ₂₂ H ₂₆ O ₄
277255	H	Bu	H	CH2CO2H	C ₂₀ H ₂₄ O ₃
277257	H	CH2CO2H	H	CH2CO2H	C ₁₈ H ₁₈ O ₅
277258	H	CH2CONH2	H	CH2CO2H	C ₁₈ H ₁₉ NO ₄
277259	H	Bu	H	CH2CONH2	C ₂₀ H ₂₅ NO ₂

SOURCE – Asahi Chemical.

REFERENCES

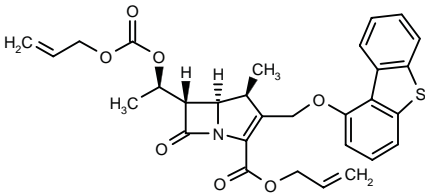
1. Shoda, M. and Itoh, H. (Asahi Chemical Industry Co., Ltd.) *Biphenyl-5-alkanoic acid derivs. and use thereof*. WO 9919291.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

275628

(1*S*,6*S*)-6-[1(*R*)-(Allyloxycarbonyloxy)ethyl]-2-(dibenzo-thiophen-1-yloxymethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid allyl ester



C30 H29 N O7 S; Mol wt: 547.6251

ACTION – Carbapenem antibiotic active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Within this series of specifically claimed compounds, the following are also included:

31. Tunn, U.W. and Melamed, R.J. *The GnRH antagonist cetrorelix as new concept for the treatment of locally confined or advanced CAP*. Aging Male 1998, 1(Suppl. 1): Abst 041.

32. Tunn, U.W. et al. *Tolerability and hormonal suppression of the LHRH-antagonist cetrorelix in patients with prostate cancer*. J Urol 1997, 157(4, Suppl.): Abst 551.

33. Verboost, P.M. et al. *Effects of GnRH-agonist and antagonist on steroid production in rat and human granulosa cells*. Gynecol Endocrinol 1999, 13(Suppl. 1): Abst 101.

34. *Annual Report: Asta Medica*. DailyDrugNews.com (Daily Essentials) 1998, March 2.

35. *Asta Medica and Nippon Kayaku established second joint venture - It develops two drugs in Japan*. Asta Medica AG Press Release 1995, June.

36. *Asta Medica files for approval of LHRH antagonist and establishes marketing partnership*. DailyDrugNews.com (Daily Essentials) 1999, Jan 14.

37. *E.U. marketing approval granted for Cetrotide*. DailyDrugNews.com (Daily Essentials) 1999, May 6.

38. *First launches announced for Asta Medica's LHRH antagonist*. DailyDrugNews.com (Daily Essentials) 1999, June 9.

39. *In development: New medicines for older Americans*. Pharmaceutical Research and Manufacturers of America 1995, July 14.

40. *Nippon Kayaku: Annual Report 1998*. DailyDrugNews.com (Daily Essentials) 1999, Jan 25.

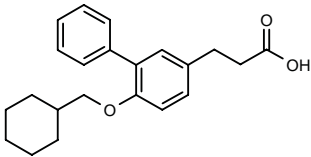
MONOGRAPH – Reissmann, T. et al. *Cetrorelix*. Drugs Fut 1994, 019(03): 0228.

*Drug Data Report 1989, 011(10): 0838.

DERMATOLOGIC DRUGS

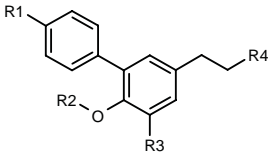
277251

3-[6-(Cyclohexylmethoxy)biphenyl-3-yl]propionic acid



C22 H26 O3; Mol wt: 338.4444

ACTION – Cytokine and IgE antibody production inhibitor; it produced 62.0% inhibition of antigen-induced IgE antibody production in the passive cutaneous anaphylaxis reaction in mice following oral dosing with 10 mg/kg/day for 5 days, and it also inhibited the production of IL-4 and IL-5 in spleen cells from sensitized mice by at least 50% at concentrations of 1-10 µg. Significant inhibition of the immediate allergic paw edema response was also observed in mice administered doses of 3-100 mg/kg/day p.o. for 5 days. It is expected to be useful in the treatment of allergic disorders. Other exemplified biphenyl-5-alkanoic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
277252	H	cyclopentyl	H	CO2H	C ₂₀ H ₂₂ O ₃
277253	H	cyclohexyl-CH2	NHCONH2	CO2H	C ₂₃ H ₂₈ N ₂ O ₄
277254	OH	cyclohexyl-CH2	H	CO2H	C ₂₂ H ₂₆ O ₄
277255	H	Bu	H	CH2CO2H	C ₂₀ H ₂₄ O ₃
277257	H	CH2CO2H	H	CH2CO2H	C ₁₈ H ₁₈ O ₅
277258	H	CH2CONH2	H	CH2CO2H	C ₁₈ H ₁₉ NO ₄
277259	H	Bu	H	CH2CONH2	C ₂₀ H ₂₅ NO ₂

SOURCE – Asahi Chemical.

REFERENCES

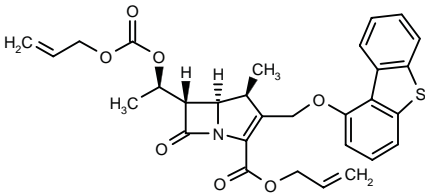
1. Shoda, M. and Itoh, H. (Asahi Chemical Industry Co., Ltd.) *Biphenyl-5-alkanoic acid derivs. and use thereof*. WO 9919291.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

275628

(1*S*,6*S*)-6-[1(*R*)-(Allyloxycarbonyloxy)ethyl]-2-(dibenzo-thiophen-1-yloxymethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid allyl ester



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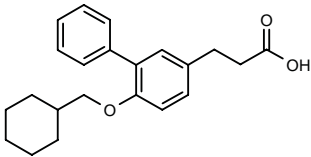
MONOGRAPH – Reissmann, T. et al. *Cetrorelix*. Drugs Fut 1994, 019(03): 0228.

*Drug Data Report 1989, 011(10): 0838.

DERMATOLOGIC DRUGS

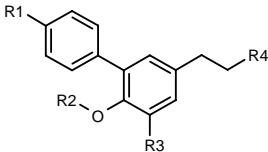
277251

3-[6-(Cyclohexylmethoxy)biphenyl-3-yl]propionic acid



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Compound	R1	R2	R3	R4	Formula
277252	H	cyclopentyl	H	CO2H	C20H22O3
277253	H	cyclohexyl-CH2	NHCONH2	CO2H	C23H28N2O4
277254	OH	cyclohexyl-CH2	H	CO2H	C22H26O4
277255	H	Bu	H	CH2CO2H	C20H24O3
277257	H	CH2CO2H	H	CH2CO2H	C18H18O5
277258	H	CH2CONH2	H	CH2CO2H	C18H19NO4
277259	H	Bu	H	CH2CONH2	C20H25NO2

SOURCE – Asahi Chemical.

REFERENCES

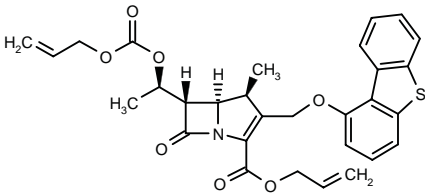
1. Shoda, M. and Itoh, H. (Asahi Chemical Industry Co., Ltd.) *Biphenyl-5-alkanoic acid derivs. and use thereof*. WO 9919291.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

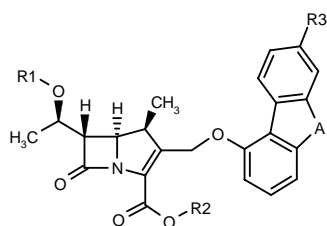
275628

(1*S*,6*S*)-6-[1(*R*)-(Allyloxycarbonyloxy)ethyl]-2-(dibenzo-thiophen-1-yloxymethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid allyl ester

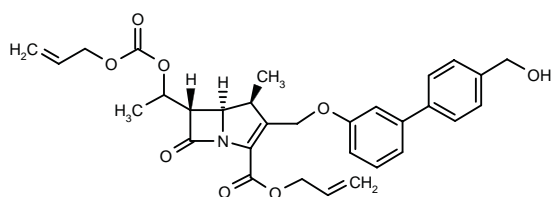


C30 H29 N O7 S; Mol wt: 547.6251

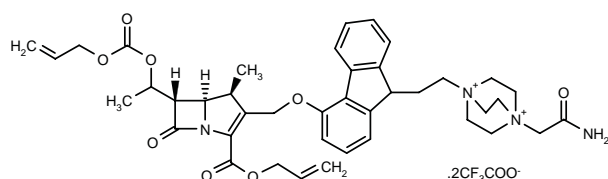
ACTION – Carbapenem antibiotic active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	R3	A	Formula
275630	H	Na	H	SO ₂	C ₂₃ H ₂₀ NNaO ₇ S
275632	H	Na	H	CH(CH ₂ CO ₂)Me	C ₂₇ H ₂₆ NNaO ₇
275634	allyl- -OCO	allyl	CH ₂ I	-CO-	C ₃₂ H ₃₀ INO ₈
275635	H	negative charge	1-Me- -3-imidazolyl-CH ₂	-CO-	C ₂₉ H ₂₇ N ₃ O ₆
275636	H	negative charge	1-Me- -3-imidazolyl-(CH ₂) ₃	-CO-	C ₃₁ H ₃₁ N ₃ O ₆
275637	H	negative charge	1-Me- -3-imidazolyl-(CH ₂) ₃	-C(=CH-CO ₂ Me)-	C ₃₄ H ₃₅ N ₃ O ₇



275631: C31 H33 N O8



275633: C41 H50 N4 O8 . 2 C2 F3 O2

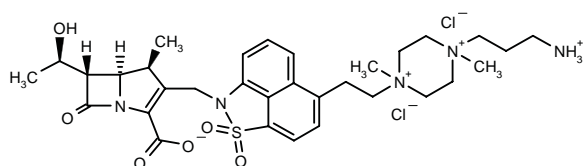
SOURCE – Merck & Co.

REFERENCES

1. Dininno, F.P. and Chen, H. (Merck & Co., Inc.) *Aryloxymethyl carbapenem antibacterials*. WO 9914217.

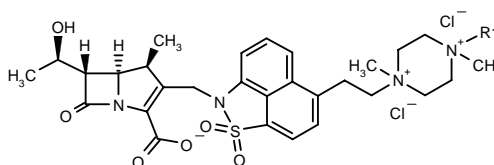
276048

(1*S*,5*R*,6*S*)-2-[6-[2-[4-(3-Ammoniopropyl)-1,4-dimethylpiperazinium-1-yl]ethyl]-1,1-dioxonaphtho[1,8-*cd*]isothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate dichloride

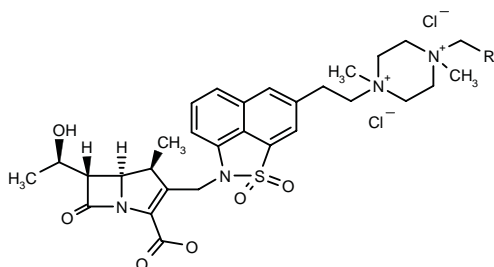


C32 H45 Cl2 N5 O6 S; Mol wt: 698.7085

ACTION – Carbapenem antibiotic active *in vitro* against Gram-positive microorganisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci, as well as Gram-negative pathogens. Other exemplified carbapenem compounds include the following:



Compound	R1	Formula
276049	CH2CH2NH3 ⁺	C ₃₁ H ₄₃ Cl ₂ N ₅ O ₆ S
276050	(CH2)4NH3 ⁺	C ₃₃ H ₄₇ Cl ₂ N ₅ O ₆ S
276051	(CH2)5NH3 ⁺	C ₃₄ H ₄₉ Cl ₂ N ₅ O ₆ S
276052	CH2CH2CH(Me)NH3 ⁺	C ₃₃ H ₄₇ Cl ₂ N ₅ O ₆ S
276053	(R)-CH2CH(Me)CH2NH3 ⁺	C ₃₃ H ₄₇ Cl ₂ N ₅ O ₆ S
276054	(CH2)3N ⁺ Me	C ₃₃ H ₄₇ Cl ₂ N ₅ O ₆ S
276055	CH2CONH(CH2)3NH3 ⁺	C ₃₄ H ₄₈ Cl ₂ N ₆ O ₇ S
276056	CH2CONHCH2CH2NH3 ⁺	C ₃₃ H ₄₆ Cl ₂ N ₆ O ₇ S
276059	4-(NH3 ⁺ CH2)-PhNHCOCH2	C ₃₈ H ₄₈ Cl ₂ N ₆ O ₇ S
276060	4-(NH3 ⁺ CH2CH2)-PhNHCOCH2	C ₃₉ H ₅₀ Cl ₂ N ₆ O ₇ S
276061	2-(NH3 ⁺ CH2CH2)-PhNHCOCH2	C ₃₉ H ₅₀ Cl ₂ N ₆ O ₇ S
276062	3-(NH3 ⁺ CH2CH2)-PhNHCOCH2	C ₃₉ H ₅₀ Cl ₂ N ₆ O ₇ S



Compound	R1	Formula
276057	CH ₂ CH ₂ NH ₃ ⁺	C ₃₂ H ₄₅ Cl ₂ N ₅ O ₆ S
276058	CH ₂ CH ₂ N ⁺ Me	C ₃₃ H ₄₇ Cl ₂ N ₅ O ₆ S
276063	4-(NH ₃ ⁺ CH ₂ CH ₂)-PhNHCO	C ₃₉ H ₅₀ Cl ₂ N ₆ O ₇ S

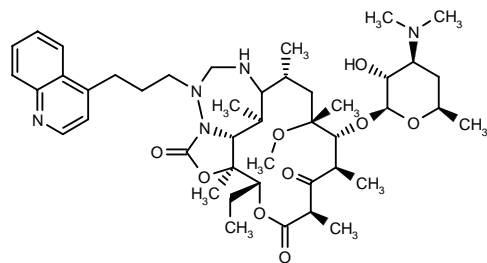
SOURCE – Merck & Co.

REFERENCES

1. Cama, L.D. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. and methods of treatment*. WO 9920627.

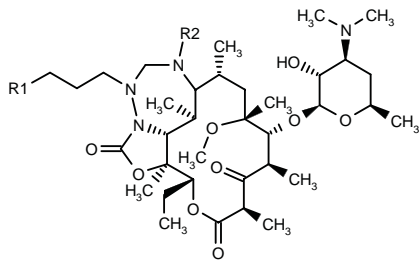
276533

9-Amino-9-deoxo-11-deoxy-3-(descladinosyloxy)-6-*O*-methyl-3-oxo-11-[2-[3-(4-quinoliny)propyl]hydrazino]-9a-*N*,11b-*N*-methyleneerythromycin A 11a-*N*,12-*O*-cyclic carbamate



C44 H67 N5 O9; Mol wt: 810.0393

ACTION – Macrolide antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, as well as protozoa. Within this series of tricyclic erythromycin derivatives, the following are also included:



Compound	R1	R2	Formula
276535	4-quinolyl	Me	C ₄₅ H ₆₉ N ₅ O ₉
276536	4-Pyr	H	C ₄₀ H ₆₅ N ₅ O ₉
276537	4-Pyr	Me	C ₄₁ H ₆₇ N ₅ O ₉
276540	4-Ph-1-imidazolyl	H	C ₄₄ H ₆₈ N ₆ O ₉
276543	4-Ph-1-imidazolyl	Me	C ₄₅ H ₇₀ N ₆ O ₉
276544	4-(3-Pyr)-1-imidazolyl	H	C ₄₃ H ₆₇ N ₇ O ₉
276545	2-benzotriazolyl	Me	C ₄₂ H ₆₇ N ₇ O ₉

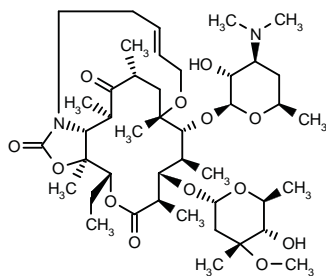
SOURCE – Pfizer.

REFERENCES

1. Wu, Y.-J. (Pfizer Products Inc.) *Tricyclic erythromycin derivs.* WO 9921865.

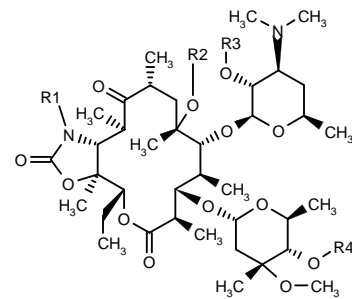
276538

11-Amino-11-desoxy-6-*O*,11-*N*-(2-pentenylene)erythromycin A 11-*N*,12-*O*-cyclic carbamate



C43 H72 N2 O13; Mol wt: 825.0428

ACTION – Macrolide antibiotic with good antibacterial activity against a range of Gram-positive bacteria and some Gram-negative pathogens, giving MIC values of 0.1-6.2 µg/ml (erythromycin A = 0.2-3.1 µg/ml) against a number of strains of *Staphylococcus aureus*, 0.05 µg/ml (erythromycin A = 0.05 µg/ml) against *Enterococcus faecium* ATCC 8043, 0.02 µg/ml (erythromycin A = 0.05 µg/ml) against *Streptococcus pyogenes* EES61, 0.78 µg/ml (erythromycin A = 0.78 µg/ml) against *Escherichia coli* SS, 0.015-8 µg/ml (erythromycin A = 0.06-16 µg/ml) against strains of *Streptococcus pneumoniae*, and 0.02-0.1 µg/ml (erythromycin A = 0.05-0.2 µg/ml) against strains of *Micrococcus luteus*. Other exemplified 6,11-bridged erythromycin derivatives include the following:



Compound	R1	R2	R3=R4	Formula
276539	-CH ₂ CH=CHCH ₂ -		Ac	C ₄₆ H ₇₄ N ₂ O ₁₅
276541	-(CH ₂) ₄ -		H	C ₄₂ H ₇₂ N ₂ O ₁₃
276542	-CH ₂ CH(OH)CH ₂ CH=CHCH ₂ -		H	C ₄₄ H ₇₄ N ₂ O ₁₄

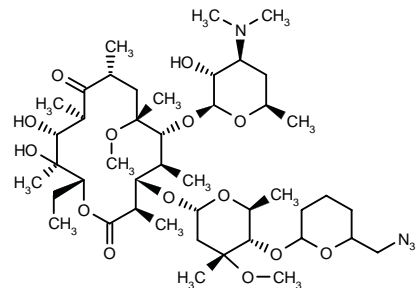
SOURCE – Abbott.

REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) *6,11-Bridged erythromycin derivs.* WO 9921864.

277234

4''-*O*-(6-Azidomethyltetrahydropyran-2-yl)-6-*O*-methyl-erythromycin A



C44 H78 N4 O14; Mol wt: 887.1142

ACTION – Macrolide antibiotic, a representative compound within a series of 4''-substituted erythromycin A derivatives, found to be active against Gram-positive bacteria including *Staphylococcus aureus* 209P-JC (MIC = 0.78 µg/ml), *S. aureus* Smith (MIC = 3.13 µg/ml), *Staphylococcus epidermidis* IID553 (MIC = 0.78 µg/ml), *Enterococcus faecalis* CSJ1212 (MIC = 1.56 µg/ml) and *Streptococcus pneumoniae* IID553 (MIC = 0.39 µg/ml).

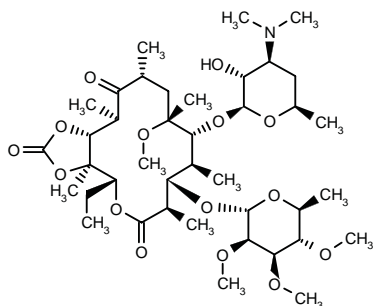
SOURCES – Sagami; Taisho.

REFERENCES

1. Kabori, T. et al. (Sagami Chemical Research Center; Taisho Pharmaceutical Co., Ltd.) 4"-Substd. erythromycin A derivs. JP 99116592.

277235

3-*O*-Deshexopyranosyl-3-*O*-(6-deoxy-2,3,4-*O*-tri-*O*-methyl- α -L-mannopyranosyl)-6-*O*-methylethromycin A 11-*O*,12-*O*-cyclic carbonate



C40 H69 N O15; Mol wt: 803.9771

ACTION – Macrolide antibiotic, a representative compound within a series of 3-substituted erythromycin A derivatives, found to be active against Gram-positive bacteria including *Staphylococcus aureus* 209P-JC (MIC = 0.78 μ g/ml), *S. aureus* Smith (MIC = 1.56 μ g/ml), *Staphylococcus epidermidis* IID553 (MIC = 0.78 μ g/ml), *Enterococcus faecalis* CSJ1212 (MIC = 0.78 μ g/ml) and *Streptococcus pneumoniae* IID553 (MIC = 0.39 μ g/ml).

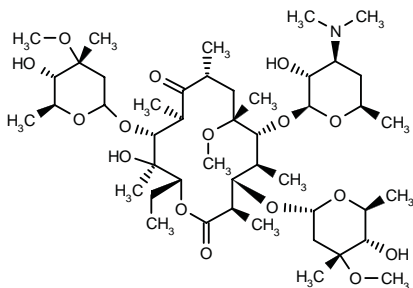
SOURCES – Sagami; Taisho.

REFERENCES

1. Asaga, T. et al. (Taisho Pharmaceutical Co., Ltd.; Sagami Chemical Research Center) 3-Substd. erythromycin A derivs. JP 99116591.

277236

11-*O*- α -Cladinosyl-6-*O*-methylethromycin A



C46 H83 N O16; Mol wt: 906.1527

ACTION – Macrolide antibiotic, a representative compound within a series of 11-substituted erythromycin A derivatives, found to be active against Gram-positive bacteria including *Staphylococcus aureus* 209P-JC (MIC = 0.39 μ g/ml), *S. aureus* Smith (MIC = 0.78 μ g/ml), *Staphylococcus epidermidis* IID553 (MIC = 0.39 μ g/ml), *Enterococcus faecalis* CSJ1212 (MIC = 1.56 μ g/ml) and *Streptococcus pneumoniae* IID553 (MIC = 0.20 μ g/ml).

SOURCES – Sagami; Taisho.

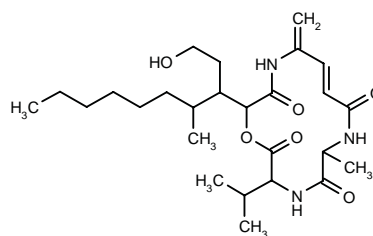
REFERENCES

1. Asaga, T. et al. (Taisho Pharmaceutical Co., Ltd.; Sagami Chemical Research Center) 11-Substd. erythromycin A derivs. JP 99116590.

VINYLAMYCIN

276596

14-[1-(2-Hydroxyethyl)-2-methyloctyl]-3-isopropyl-6-methyl-11-methylene-1-oxa-4,7,12-triazacyclotetradec-9-ene-2,5,8,13-tetraone



C26 H43 N3 O6; Mol wt: 493.6407

ACTION – Antibiotic isolated from a culture of *Streptomyces* sp. MI 982-63 F1 strain (FERM P-16404), active against Gram-positive bacteria, including drug-resistant strains. *In vitro*, it exhibited MIC values of 1.56 and 3.13 μ g/ml against *Staphylococcus aureus* FDA 209P and methicillin-resistant *S. aureus* (MRSA) No. 5, respectively.

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Igarashi, M. et al. (Microbial Chemistry Research Foundation) Antibiotic vinylamycin and its preparation method. JP 99103886.

ANTIBACTERIAL DRUGS

276409

Alligator hemoglobin heme-free α -chain

ACTION – Heme-free hemoglobin α -chain from *Alligator mississippiensis* with antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi such as *Escherichia coli* (MIC = 10-20 μ g/ml), *Pseudomonas aeruginosa* (MIC = 25-100 μ g/ml) and *Candida albicans* (MIC = 20-30 μ g/ml).

SOURCE – Theragem.

REFERENCES

1. Hoffman, B.F. and Binah, O. (Theragem, Inc.) Reptilian-derived peptides for the treatment of microbial infection. WO 9917785.

276411*Human hemoglobin heme-free α 3-chain*

ACTION – Fragment of the human heme-free hemoglobin α -chain with antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi such as *Escherichia coli* (MIC = 5-8 μ g/ml), *Streptococcus faecalis* (MIC = 7 μ g/ml) and *Candida albicans* (MIC = 10-50 μ g/ml). Another peptide from this series of derivatives of mammalian hemoglobin with antimicrobial activity is:

*Human hemoglobin heme-free β 2-chain***276412**

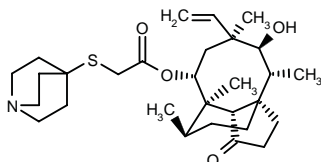
SOURCE – Theragem.

REFERENCES

- Hoffman, B.F. and Dubnick, B. (Theragem, Inc.) *Mammalian-derived peptides for the treatment of microbial infection*. WO 9917786.

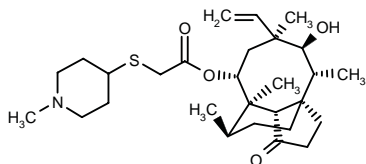
276524

(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*S*,10*R*)-2-(Quinuclidin-4-ylsulfanyl)acetic acid 5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3a,9-propanocyclopentacycloocten-8-yl ester

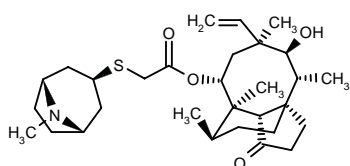


C29 H45 N O4 S; Mol wt: 503.7435

ACTION – Antimicrobial pleuromutilin derivative with improved antibacterial properties compared to parent compound. Potentially useful for the treatment of infections caused by, for example, Gram-positive and Gram-negative bacteria and *Mycoplasma* including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* spp., *Neisseria* spp., *Legionella* spp., *Chlamydia* spp., *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*. Its use in the prophylaxis of recurrent otitis media or recurrent acute bacterial sinusitis, as well as skin and soft tissue infections and acne, is specifically claimed. Other representative compounds are:



276525: C28 H45 N O4 S



276526: C30 H47 N O4 S

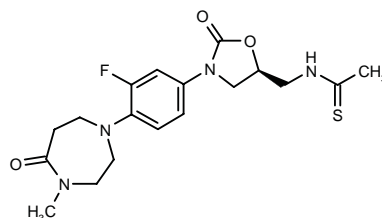
SOURCE – SmithKline Beecham.

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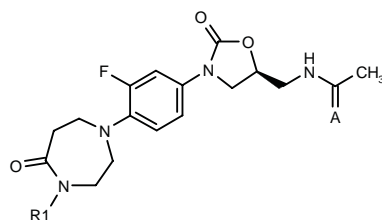
276801

N-[3-[3-Fluoro-4-(4-methyl-5-oxoperhydro-1,4-diazepin-1-yl)phenyl]-2-oxooxazolidin-5-(*S*)-ylmethyl]thioacetamide



C18 H23 F N4 O3 S; Mol wt: 394.4687

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 9213 (MIC = 1 μ g/ml), *Staphylococcus epidermidis* 12084 (MIC < 0.5 μ g/ml), *Enterococcus faecalis* 9217 (MIC = 1 μ g/ml), *Streptococcus pneumoniae* 9912 (MIC < 0.5 μ g/ml), *Haemophilus influenzae* 30063 (MIC = 8 μ g/ml) and *Moraxella catarrhalis* 30610 (MIC = 2 μ g/ml). Other specifically claimed compounds from this series of 4-(1,4-diazepin-1-yl)phenyl-substituted oxazolidinone derivatives include the following:



Compound	R1	A	Formula
276802	H	O	C ₁₇ H ₂₁ FN ₄ O ₄
276803	H	S	C ₁₇ H ₂₁ FN ₄ O ₃ S
276805	Me	O	C ₁₈ H ₂₃ FN ₄ O ₄

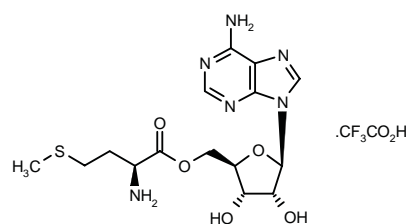
SOURCE – Pharmacia & Upjohn.

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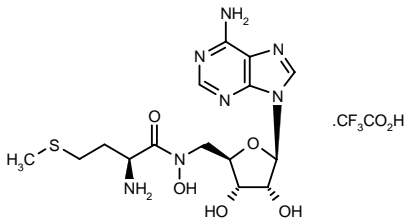
277056

L-Methionine adenosine-5'-*O*-yl ester trifluoroacetate



C15 H22 N6 O5 S . C2 H F3 O2; Mol wt: 512.4637

ACTION – Antibacterial agent, a strong inhibitor of methionyl-tRNA synthetase isolated from *Escherichia coli* ($K_i = 10.9 \mu\text{M}$), *Mycobacterium tuberculosis*, *Saccharomyces cerevisiae* and human cells. Compound exhibited strong growth inhibition of *E. coli* (MIC = 0.5 $\mu\text{g/ml}$) and moderate inhibition of *Bacillus cereus* (MIC = 32 $\mu\text{g/ml}$). Another related methionyl adenylate analogue is:



277057: C15 H23 N7 O5 S . C2 H F3 O2

SOURCE – ImaGene.

REFERENCES

1. Lee, J. et al. *Methionyl adenylate analogues as inhibitors of methionyl-tRNA synthetase*. Bioorg Med Chem Lett 1999, 9(10): 1365.

277351

L-Arginyl-glycyl-glycyl-L-arginyl-L-threonyl-L-cysteinyl-L-cysteinyl-L-phenylalanyl-L-arginyl-L-arginyl-L-arginyl-L-cysteinyl-L-tyrosyl-L-valyl-L-cysteinyl-L-valyl-glycyl-L-arginine

C86 H146 N36 O21 S4; Mol wt: 2148.5940

ACTION – Antimicrobial peptide related to naturally occurring protegrin peptides with a broad spectrum of activity against bacteria, fungi, protozoa and certain strains of viruses, and a low frequency of resistance; it also exhibits improved serum compatibility and decreased hemolytic activity against human red blood cells as compared to native PG-1 and melittin. *In vitro*, compound exhibited comparable or improved antimicrobial activity compared to PG-1 against *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Listeria monocytogenes*. In addition, it exhibited lower cytotoxicity than native PG-1 and melittin, as demonstrated in an MTT assay against human cervical carcinoma ME-180 cells by EC_{50} values of 101.3, 47.2 and 8.0 $\mu\text{g/ml}$, respectively. Other peptides from this series of threonine-containing protegrins include the following:

L-Arginyl-glycyl-glycyl-L-arginyl-L-leucyl-L-cysteinyl-L-threonyl-L-cysteinyl-L-arginyl-L-arginyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-valyl-L-cysteinyl-L-valyl-glycyl-L-arginine

277352: C83 H148 N36 O20 S4

L-Arginyl-glycyl-glycyl-L-arginyl-L-leucyl-L-cysteinyl-L-tyrosyl-L-cysteinyl-L-arginyl-L-arginyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-threonyl-L-cysteinyl-L-valyl-glycyl-L-arginine

277354: C87 H148 N36 O21 S4

L-Arginyl-glycyl-glycyl-L-arginyl-L-leucyl-L-cysteinyl-L-tyrosyl-L-cysteinyl-L-arginyl-L-arginyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-valyl-L-cysteinyl-L-threonyl-glycyl-L-arginine

277355: C87 H148 N36 O21 S4

SOURCE – IntraBiotics.

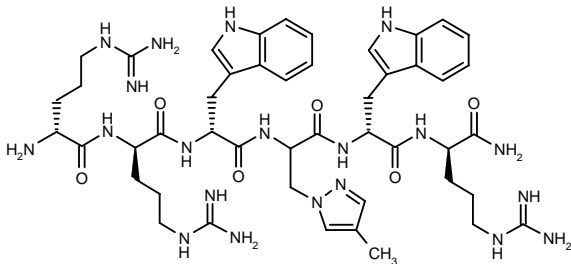
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ANTIFUNGAL AGENTS

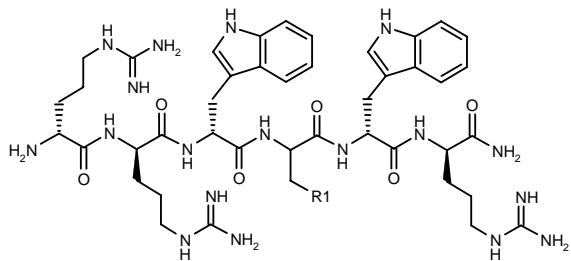
276597

D-Arginyl-D-arginyl-D-tryptophyl-DL-3-(4-methylpyrazol-1-yl)alanyl-D-tryptophyl-D-argininamide



C47 H68 N20 O6; Mol wt: 1009.1880

ACTION – Antifungal agent with MIC values of 12.5, 1.56, 12.5 and 25 $\mu\text{g/ml}$ against *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*, respectively. Other exemplified peptides include the following:



Compound	R1	Isomer	Formula
276598	1-pyrazolyl	DL	C ₄₆ H ₆₆ N ₂₀ O ₆
276599	1,2,4-triazol-1-yl	DL	C ₄₅ H ₆₅ N ₂₁ O ₆
276600	1,2,3-triazol-1-yl	DL	C ₄₅ H ₆₅ N ₂₁ O ₆
276601	4-Br-1-pyrazolyl	DL	C ₄₆ H ₆₅ BrN ₂₀ O ₆
276602	1-benzotriazolyl	DL	C ₄₉ H ₆₉ N ₂₁ O ₆
276603	4-imidazolyl	D	C ₄₆ H ₆₆ N ₂₀ O ₆

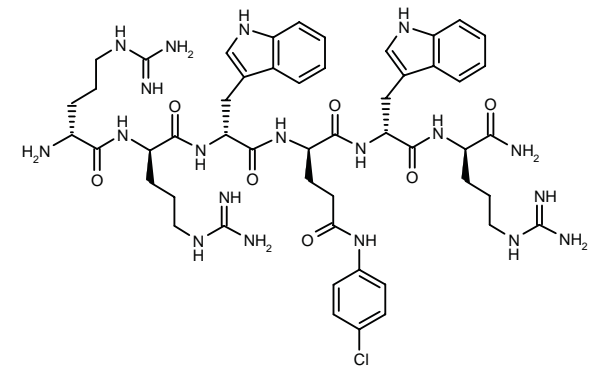
SOURCE – Morinaga Milk.

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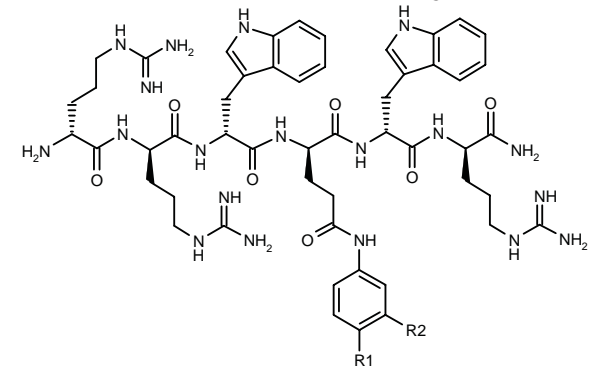
276618

D-Arginyl-D-arginyl-D-tryptophyl-D-[N⁵-(4-chlorophenyl)]-glutamyl-D-tryptophyl-D-argininamide



C51 H70 Cl N19 O7; Mol wt: 1096.6930

ACTION – Antifungal agent with MIC values of 6.25, 3.13, 12.5 and 12.5 µg/ml against *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*, respectively. LD₅₀ = 500 mg/kg p.o. or more in mice. Other exemplified peptides include the following:



Compound	R1	R2	Formula
276619	Br	H	C ₅₁ H ₇₀ BrN ₁₉ O ₇
276620	F	H	C ₅₁ H ₇₀ FN ₁₉ O ₇
276621	H	Me	C ₅₂ H ₇₃ N ₁₉ O ₇
276622	OMe	H	C ₅₂ H ₇₃ N ₁₉ O ₈

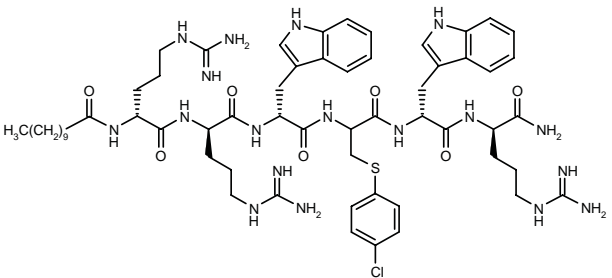
SOURCE – Morinaga Milk.

REFERENCES

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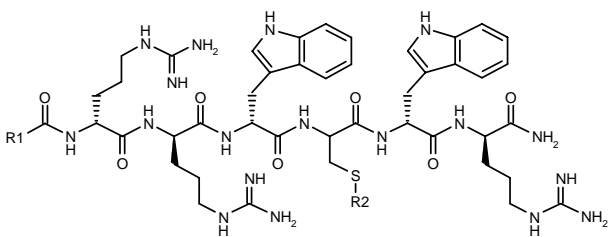
277278

Undecanoyl-D-arginyl-D-arginyl-D-tryptophyl-DL-[S-(4-chlorophenyl)]cysteinyl-D-triptyophyl-D-arginamide



C60 H87 Cl N18 O7 S; Mol wt: 1239.9850

ACTION – Antifungal peptide with MIC values of 12.5, 3.13, 12.5 and 6.25 µg/ml against *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*, respectively. Other exemplified peptides include the following:



Compound	R1	R2	Formula
277279	C5H11	4-Cl-Ph	C ₅₅ H ₇₇ ClN ₁₈ O ₇ S
277280	C9H19	4-Cl-Ph	C ₅₉ H ₈₆ ClN ₁₈ O ₇ S
277281	C11H23	4-Cl-Ph	C ₆₁ H ₈₈ ClN ₁₈ O ₇ S
277282	allyl-(CH2)7	4-Cl-Ph	C ₆₀ H ₇₇ ClN ₁₈ O ₇ S
277283	ethynyl-(CH2)8	4-Cl-Ph	C ₆₀ H ₇₅ ClN ₁₈ O ₇ S
277284	C10H21	4-Cl-PhCH2	C ₆₁ H ₈₈ ClN ₁₈ O ₇ S

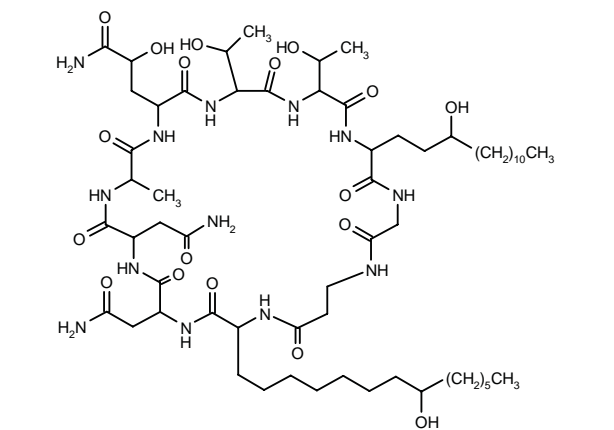
SOURCE – Morinaga Milk.

REFERENCES

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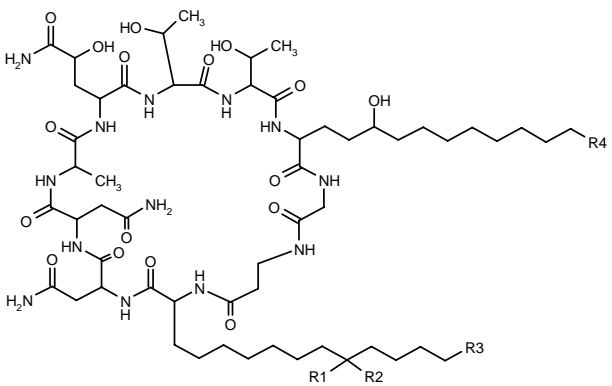
277303

3-[5,8-Bis(carbamoylmethyl)-17,20-bis(1-hydroxyethyl)-23-(3-hydroxytetradecyl)-2-(8-hydroxytetradecyl)-11-methyl-3,6,9,12,15,18,21,24,27,31-decaoxo-1,4,7,10,13,16,19,22,25,28-decaazacyclohentriacontan-14-yl]-2-hydroxypropionamide



C61 H109 N13 O18; Mol wt: 1312.6050

ACTION – Antifungal agent isolated from fungal strain SANK 17397 (FERM BP-6123), active *in vitro* against yeasts such as *Candida albicans* ATCC 90029 (MIC = 0.5 µg/ml), *Candida parapsilosis* ATCC 90018 (MIC = 0.25 µg/ml) and *Candida tropicalis* SANK 59263 (MIC = 2 µg/ml), while being inactive against *Cryptococcus neoformans* SANK 59863 (MIC > 64 µg/ml) and *Aspergillus fumigatus* SANK 10662 (MIC > 64 µg/ml). Compound was found to inhibit 1,3-β-glucan synthase from *A. fumigatus* with an IC₅₀ of 0.012 µg/ml. Other compounds isolated from this source are:



Compound	R1	R2	R3	R4	Formula
277305	H	OH	H	Me	C ₅₇ H ₁₀₁ N ₁₃ O ₁₈
277306	H	OH	Et	Me	C ₅₉ H ₁₀₅ N ₁₃ O ₁₈
277307	H	OH	Me	Me	C ₅₈ H ₁₀₃ N ₁₃ O ₁₈
277308	-O-		Et	Me	C ₅₈ H ₁₀₃ N ₁₃ O ₁₈
277309	H	OH	Et	Et	C ₆₀ H ₁₀₇ N ₁₃ O ₁₈

SOURCE – Sankyo.

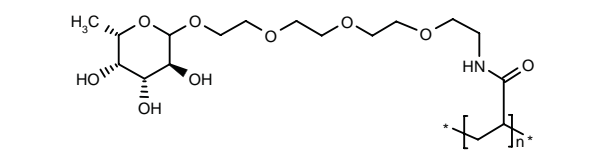
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ANTIVIRAL DRUGS

275389

Poly[*N*-[11-(6-deoxy-*L*-galactopyranosyloxy)-3,6,9-trioxundec-1-yl]acrylamide]



C17 H31 N O9; Mol wt: 393.4299

ACTION – Agent for the treatment or prevention of rotavirus infections shown to produce 76-100% inhibition of infection in suckling mice when given at a concentration of 5% w/w p.o. t.i.d. x 4 days starting at day 1 postinfection. A representative compound from a series of polymers comprising one or more fucoside moieties.

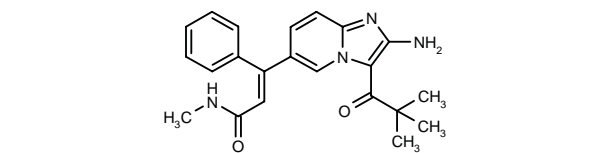
SOURCE – GelTex.

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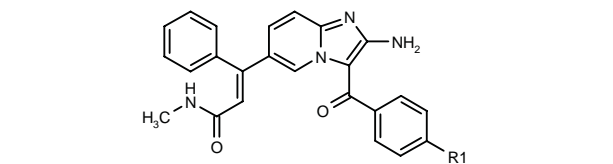
277036

3-[2-Amino-3-(pivaloyl)imidazo[1,2-*a*]pyridin-6-yl]-*N*-methyl-3-phenyl-2(*E*)-propenamide



C22 H24 N4 O2; Mol wt: 376.4576

ACTION – Antiviral agent active against human rhinovirus-14 (HRV-14; IC₅₀ = 0.17 µg/ml) and with low cytotoxicity (TC₅₀ > 10 µg/ml) and a good therapeutic index (> 60). Other imidazo[1,2-*a*]pyridines with a similar profile of activity are:



Compound	R1	Formula
277034	H	C ₂₄ H ₂₀ N ₄ O ₂
277035	F	C ₂₄ H ₁₉ FN ₄ O ₂

SOURCE – Lilly.

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ZANAMIVIR⁺

Prop INN; BAN; USAN

191315

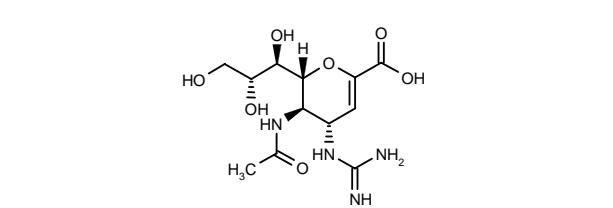
N-Acetyl-2,3-didehydro-4-deoxy-4-guanidinoneuraminic acid

5-Acetamido-2,3-didehydro-3,4,5-trideoxy-4-guanidino- α -D-*glycero*-D-*galacto*-2-nonulopyranosonic acid

4-Guanidino-Neu5Ac2en

GG-167

GR-121167X



C12 H20 N4 O7; Mol wt: 332.3160

White crystalline powder.

ACTION – Antiviral agent, a potent and highly selective influenza neuraminidase inhibitor that acts extracellularly to inhibit the release of infective influenza virions from the epithelial cells of the respiratory tract, thereby reducing the replication of both influenza A and B viruses.

INDICATIONS – Treatment of influenza A and B virus infections in adults and children aged 12 and up.

PRESENTATION – Circular foil disk with four regularly distributed blisters containing 5 mg zanamivir. Each Relenza™ Rotadisk is inserted into the accompanying Diskhaler device and the medication is then inhaled through the mouth using the Diskhaler.

PROPRIETARY NAME – Relenza (AU).

SOURCES – Biota; Glaxo Wellcome.

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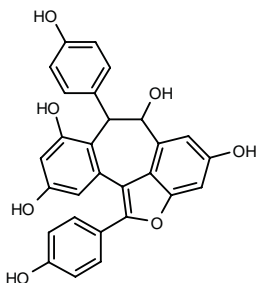
MONOGRAPH – Fromtling, R. and Castañer, J. *Zanamivir.* Drugs Fut 1996, 021(04): 0375.

*Drug Data Report 1993, 017(05): 0463.

AIDS MEDICINES

276584

1,7-Bis(4-hydroxyphenyl)-6,7-dihydrobenzo[6,7]-cyclohepta[1,2,3-*cd*][1]benzofuran-4,6,8,10-tetraol



C₂₈ H₂₀ O₇; Mol wt: 468.4590

ACTION – Antiviral agent for AIDS with HIV protease-inhibitory activity (IC₅₀ = 13 μM) and anti-HIV activity in infected MT-4 cells (IC₅₀ = 52 μM).

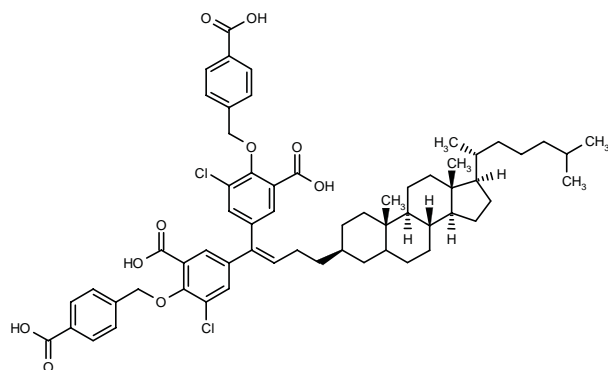
SOURCE – Sankyo.

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277042

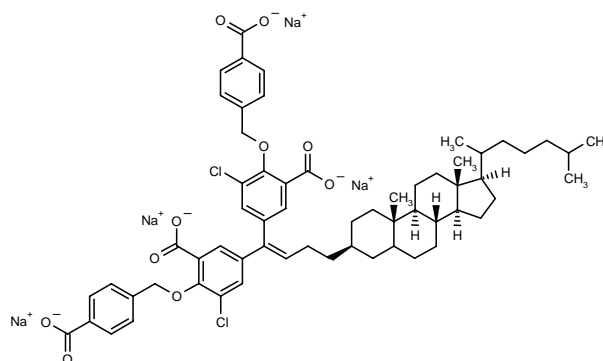
3β-[4,4-Bis[3-Carboxy-4-(4-carboxybenzyloxy)-5-chlorophenyl]-3-buten-1-yl]cholestane



C₆₁ H₇₂ Cl₂ O₁₀; Mol wt: 1036.1360

White solid, *m.p.* 223-5 °C.

ACTION – Anti-HIV agent, an analogue of cosalane proven to inhibit the cytopathicity of HIV-1_{RF} in CEM-SS cells and of HIV-1_{IIIB} in MT-4 cells with EC₅₀ values of 0.5 and 1.7 μM, respectively. Compound was less potent against HIV-2_{ROD} (EC₅₀ = 22 μM) in MT-4 cells and exhibited relatively low cytotoxicity (CC₅₀ = 72 and 88 μM, respectively, in CEM-SS and MT-4 cells), and it showed little or no inhibitory activity against reverse transcriptase, integrase and protease. The anti-HIV action of the compound appears to be mediated at least in part by binding to CD4 and the consequent inhibition of gp120 binding to the cell, as well as by preventing the proper association of the gp120-CD4 complex with the CXCR4 receptor. Another potent cosalane derivative is:



277043: C₆₁ H₆₈ Cl₂ Na₄ O₁₀

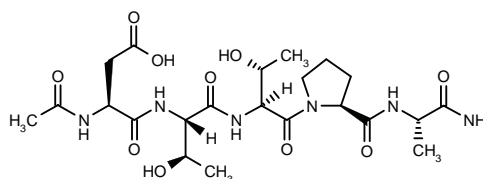
SOURCES – National Cancer Institute, Bethesda, MD (US); Purdue University, West Lafayette, IN (US); Rega Institute for Medical Research, Leuven (BE).

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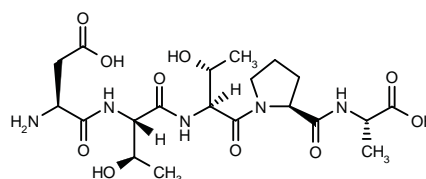
277061

N-Acetyl-L-aspartyl-L-threonyl-L-threonyl-L-prolyl-L-alaninamide



C₂₂ H₃₆ N₆ O₁₀; Mol wt: 544.5584

ACTION – Anti-HIV-1 agent, a low-molecular-weight peptide derived from the amino-terminal sequence of RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) proven to exert antiviral activity in phytohemagglutinin-activated peripheral blood mononuclear cells infected with macrophage-tropic HIV-1 (43 and 46% inhibition at 10 and 100 nM, respectively). Another related compound is:



277060: C₂₀ H₃₃ N₅ O₁₀

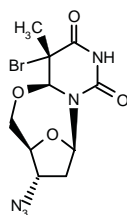
SOURCES – Seikei University, Tokyo (JP); Tokyo Medical Dental University, Tokyo (JP).

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277387

(-)-(3*S*,4*S*,6*R*,11*S*,11*Sa*)-4-Azido-11-bromo-11-methyl-3,6-epoxyperhydropyrimido[6,1-*b*][1,3]oxazine-8,10-dione



C10 H12 Br N5 O4; Mol wt: 346.1398

ACTION – Anti-HIV agent, an analogue of zidovudine (AZT) proven to retain the potency of the parent compound against HIV-1_{IIIB} in MT-4 cells and peripheral blood mononuclear cells (IC₅₀ = 0.008 and 0.001 μM, respectively, vs. 0.007 and 0.002 μM, respectively, for AZT). Compound also showed a similar selectivity index to AZT but 55.5-fold greater lipophilicity, offering the advantage of wider distribution throughout the body and higher brain levels.

SOURCES – Universidad de Buenos Aires, Buenos Aires (AR); Universidad Nacional de Cordoba, Cordoba (AR).

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AMPRENAVIR

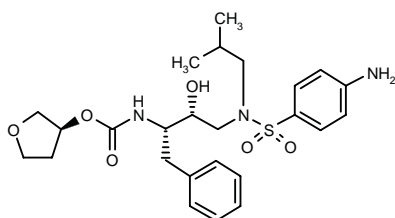
Prop INN

205414

4-Amino-*N*-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[tetrahydrofuran-3(*S*)-yloxycarbonylamino]butyl]-*N*-isobutylbenzene-sulfonamide

N-[3-(4-Amino-*N*-isobutylphenylsulfonamido)-1(*S*)-benzyl-2(*R*)-hydroxypropyl]carbamic acid tetrahydrofuran-3(*S*)-yl ester

141W94
KVX-478
VX-478⁺



C25 H35 N3 O6 S; Mol wt: 505.6380

ACTION – Anti-HIV agent, a protease inhibitor suitable for twice-daily dosing.

INDICATION – For use in combination with other antiretroviral medications in the treatment of HIV infection in treatment-experienced or -naïve adults and children.

PRESENTATION – Capsules, 50 and 150 mg; oral solution, 15 mg/ml.

PROPRIETARY NAME – Agenerase (US).

SOURCES – Glaxo Wellcome; Vertex.

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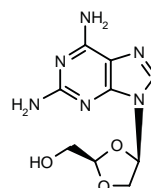
MONOGRAPH – Painter, G.R. et al. 141W94. Drugs Fut 1996, 021(04): 0347.

*Drug Data Report 1995, 017(03): 0282.

DAPD

257988

(2*R*,4*R*)-4-(2,6-Diamino-9*H*-purin-9-yl)-2-(hydroxymethyl)-1,3-dioxolane



C₉ H₁₂ N₆ O₃; Mol wt: 252.2328

ACTION – Nucleoside reverse transcriptase inhibitor with potent and selective antiviral activity against HIV-1 (EC₅₀ = 0.03 μM in human peripheral blood mononuclear cells) and hepatitis B virus (HBV; IC₅₀ = 0.023 μM in 2.2.15 cells); no cytotoxicity was observed in various cell lines at concentrations of > 100 μM. Compound showed synergistic activity with a number of other antiviral agents such as interferon alfa, 3TC (lamivudine), (–)-FTC (emtricitabine) and AZT (zidovudine). Pharmacokinetic studies have demonstrated that the majority of compound is converted to dioxolane guanosine, the active antiviral agent. It is currently in phase I/II trials for the treatment of HIV.

SOURCES – Abbott; Triangle.

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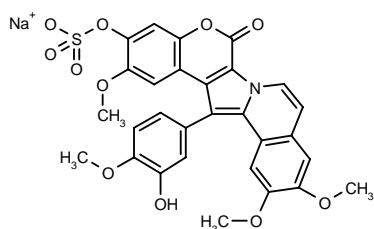
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LAMELLARIN α 20-SULFATE SODIUM SALT

277076

14-(3-Hydroxy-4-methoxyphenyl)-2,11,12-trimethoxy-3-(sulfooxy)-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one sodium salt



C29 H22 N Na O11 S; Mol wt: 615.5448

White solid, m.p. 145-8 °C.

ACTION – Anti-HIV agent, a marine natural product that acts by inhibiting HIV-1 integrase (IC_{50} = 16 and 22 μ M, respectively, against terminal cleavage activity and strand transfer activity) without affecting topoisomerase I. Compound showed inhibitory activity against the integrase catalytic domain at higher concentrations (IC_{50} = 64 μ M) and inhibited integration by preintegration complexes (IC_{50} = 88 μ M). Wild-type HIV was inhibited in cell culture with an IC_{50} of 8 μ M and cytotoxicity was low (LD_{50} = 274 μ M).

SOURCES – Indian Institute of Chemical Technology, Hyderabad (IN); Salk Institute for Biological Studies, La Jolla, CA (US); Scripps Institution of Oceanography, La Jolla, CA (US).

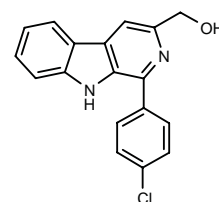
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TREATMENT OF HELMINTHIC DISEASES

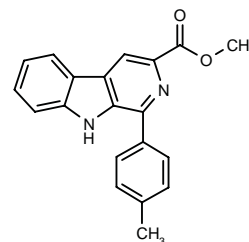
276770

1-(4-Chlorophenyl)-3-(hydroxymethyl)-9H-pyrido[3,4-b]indole

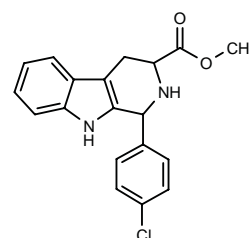


C18 H13 Cl N2 O; Mol wt: 308.7667

ACTION – Antifilarial agent with *in vivo* micro- and macrofilaricidal activity against *Acanthoeilonema vitae* (50 mg/kg i.p. x 5 days), *Litomosoides carinii* (30 mg/kg i.p. x 5 days) and *Brugia malayi* (50 mg/kg i.p. x 5 days or 250 mg/kg p.o. x 5 days). It is expected to interact with GABA receptors, suggesting a new target for antifilarial agents. Other potent β -carbolines are:



276768: C20 H16 N2 O2



276769: C19 H17 Cl N2 O2

SOURCE – Central Drug Research Institute, Lucknow (IN).

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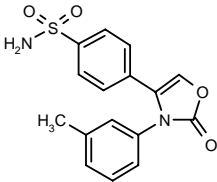
2. Srivastava, S.K. et al. *Potent 1,3-disubstituted-9H-pyrido[3,4-b]indoles as new lead compounds in antifilarial chemotherapy.* J Med Chem 1999, 42(9): 1667.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

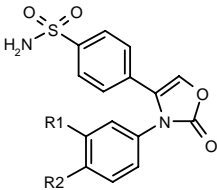
275524

4-[3-(3-Methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide



C16 H14 N2 O4 S; Mol wt: 330.3626

ACTION – Antiinflammatory agent with reduced potential for inducing gastrointestinal side effects, a selective inhibitor of cyclooxygenase type 2 (COX-2) relative to COX-1, as demonstrated in human whole blood assays (IC₅₀ = 0.51 μM vs. 6.6 μM; ratio COX-1/COX-2 = 12.9). Compound produced 57% inhibition of inflammation in the rat adjuvant arthritis model at a dose of 1 mg/kg p.o. once daily for 7 days (indomethacin: 64% inhibition at the same dose). No perforated or nonperforated ulcers were observed in rats treated orally at a dose of 100 mg/kg once daily for 4 consecutive days, whereas indomethacin was associated with marked lesions at 10 mg/kg p.o. in the same model. Other representative compounds within this series of 2(3*H*)-oxazolone derivatives include the following:



Compound	R1	R2	Formula
275525	H	H	C ₁₅ H ₁₂ N ₂ O ₄ S
275526	F	OMe	C ₁₆ H ₁₃ FN ₂ O ₅ S
275527	Cl	OMe	C ₁₆ H ₁₃ ClN ₂ O ₅ S

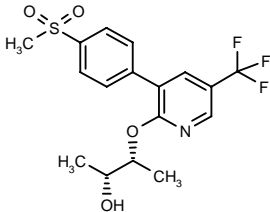
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Puig Duran, C. et al. (Almirall Prodesfarma SA) *New 2-(3H)-oxazolone derivs.* WO 9914205.

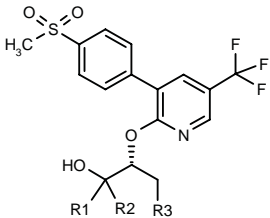
275699

3(*R*)-[3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)-2-pyridinyloxy]-2(*R*)-butanol



C17 H18 F3 N O4 S; Mol wt: 389.3922

ACTION – Antiinflammatory agent with reduced potential for inducing gastrointestinal side effects by virtue of its selective inhibition of cyclooxygenase type 2 (COX-2) relative to COX-1, as demonstrated in human whole blood (IC₅₀ COX-2 = 0.5 μM vs. > 100 μM for COX-1) and in transfected CHO cells (IC₅₀ COX-2 = 0.05 μM) and U937 cells (IC₅₀ COX-1 > 10 μM). Within this series of specifically claimed 2,3,5-trisubstituted pyridine derivatives, the following are also included:



Compound	R1	R2	R3	Isomer	Formula
275700	Me	Me	H		C ₁₈ H ₂₀ F ₃ NO ₄ S
275701	Et	Et	H		C ₂₀ H ₂₄ F ₃ NO ₄ S
275702	H	H	H		C ₁₈ H ₁₆ F ₃ NO ₄ S
275703	Me	-(CH2)2-		(+)	C ₁₉ H ₂₀ F ₃ NO ₄ S
275704	Me	-(CH2)2-		(-)	C ₁₉ H ₂₀ F ₃ NO ₄ S

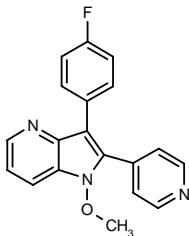
SOURCE – Merck Frosst.

REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) *2,3,5-Trisubstd. pyridines as inhibitors of cyclooxygenase-2.* WO 9914194.

276017

3-(4-Fluorophenyl)-1-methoxy-2-(4-pyridinyl)-1*H*-pyrrolo-[3,2-*b*]pyridine



C19 H14 F N3 O; Mol wt: 319.3376

SOURCE – Central Drug Research Institute, Lucknow (IN).

REFERENCES

1. Srivastava, S.K. et al. *Potent 1,3-disubstituted-9H-pyrido[3,4-b]indoles as new lead compounds in antifilarial chemotherapy.* Bioorg Med Chem 1999, 7(6): 1223.

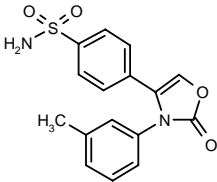
2. Srivastava, S.K. et al. *Potent 1,3-disubstituted-9H-pyrido[3,4-b]indoles as new lead compounds in antifilarial chemotherapy.* J Med Chem 1999, 42(9): 1667.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

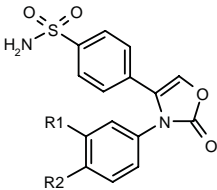
275524

4-[3-(3-Methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide



C16 H14 N2 O4 S; Mol wt: 330.3626

ACTION – Antiinflammatory agent with reduced potential for inducing gastrointestinal side effects, a selective inhibitor of cyclooxygenase type 2 (COX-2) relative to COX-1, as demonstrated in human whole blood assays (IC₅₀ = 0.51 μM vs. 6.6 μM; ratio COX-1/COX-2 = 12.9). Compound produced 57% inhibition of inflammation in the rat adjuvant arthritis model at a dose of 1 mg/kg p.o. once daily for 7 days (indomethacin: 64% inhibition at the same dose). No perforated or nonperforated ulcers were observed in rats treated orally at a dose of 100 mg/kg once daily for 4 consecutive days, whereas indomethacin was associated with marked lesions at 10 mg/kg p.o. in the same model. Other representative compounds within this series of 2(3*H*)-oxazolone derivatives include the following:



Compound	R1	R2	Formula
275525	H	H	C ₁₅ H ₁₂ N ₂ O ₄ S
275526	F	OMe	C ₁₆ H ₁₃ FN ₂ O ₅ S
275527	Cl	OMe	C ₁₆ H ₁₃ ClN ₂ O ₅ S

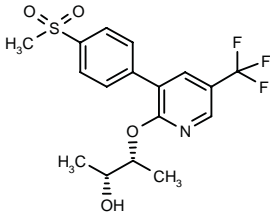
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Puig Duran, C. et al. (Almirall Prodesfarma SA) *New 2-(3H)-oxazolone derivs.* WO 9914205.

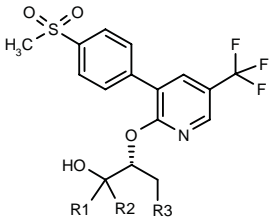
275699

3(*R*)-[3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)-2-pyridinyloxy]-2(*R*)-butanol



C17 H18 F3 N O4 S; Mol wt: 389.3922

ACTION – Antiinflammatory agent with reduced potential for inducing gastrointestinal side effects by virtue of its selective inhibition of cyclooxygenase type 2 (COX-2) relative to COX-1, as demonstrated in human whole blood (IC₅₀ COX-2 = 0.5 μM vs. > 100 μM for COX-1) and in transfected CHO cells (IC₅₀ COX-2 = 0.05 μM) and U937 cells (IC₅₀ COX-1 > 10 μM). Within this series of specifically claimed 2,3,5-trisubstituted pyridine derivatives, the following are also included:



Compound	R1	R2	R3	Isomer	Formula
275700	Me	Me	H		C ₁₈ H ₂₀ F ₃ NO ₄ S
275701	Et	Et	H		C ₂₀ H ₂₄ F ₃ NO ₄ S
275702	H	H	H		C ₁₈ H ₁₆ F ₃ NO ₄ S
275703	Me	-(CH2)2-		(+)	C ₁₉ H ₂₀ F ₃ NO ₄ S
275704	Me	-(CH2)2-		(-)	C ₁₉ H ₂₀ F ₃ NO ₄ S

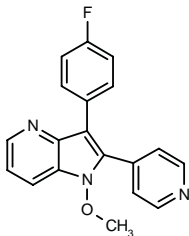
SOURCE – Merck Frosst.

REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) *2,3,5-Trisubstd. pyridines as inhibitors of cyclooxygenase-2.* WO 9914194.

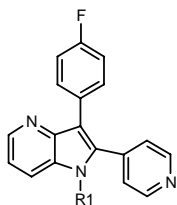
276017

3-(4-Fluorophenyl)-1-methoxy-2-(4-pyridinyl)-1*H*-pyrrolo-[3,2-*b*]pyridine

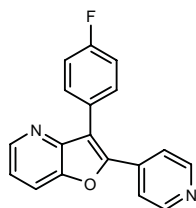


C19 H14 F N3 O; Mol wt: 319.3376

ACTION – Antiinflammatory agent, a p38 MAP kinase inhibitor (IC_{50} = 68 nM) found to inhibit the lipopolysaccharide (LPS)-induced production of tumor necrosis factor- α (TNF- α) both *in vitro* (IC_{50} = 0.46 nM in THP-1 cells) and *in vivo* in mice (75% inhibition at 30 mg p.o.). Within this series of bicyclic derivatives, the following are also included:



Compound	R1	Formula
276018	4-morpholinyl-CH ₂ CH ₂ O	C ₂₄ H ₂₃ FN ₄ O ₂
276019	1-pyrrolidinyl-CH ₂ CH ₂ O	C ₂₄ H ₂₃ FN ₄ O
276020	H	C ₁₈ H ₁₂ FN ₃
276021	1-Pip-CH ₂ CH ₂	C ₂₅ H ₂₅ FN ₄



276022: C₁₈ H₁₁ F N₂ O

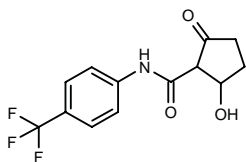
SOURCE – Roche.

REFERENCES

1. Cheng, S. et al. (F. Hoffmann-La Roche AG) *Bicyclic kinase inhibitors*. WO 9920624.

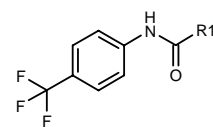
276639

2-Hydroxy-5-oxo-*N*-[4-(trifluoromethyl)phenyl]cyclopentanecarboxamide



C₁₃ H₁₂ F₃ N O₃; Mol wt: 287.2358

ACTION – Immunosuppressive and antiinflammatory agent, an analogue of the active metabolite of leflunomide A-771726. *In vitro*, compound inhibited the mixed lymphocyte reaction (MLR) in murine splenocytes with an IC_{50} value of 1.25 ± 0.2 μ M, being more potent than leflunomide (IC_{50} = 9.6 ± 3.1 μ M). It was also more potent than leflunomide in inhibiting the expression of CD2, CD25 and CD71 lymphocyte activation antigens in human peripheral blood mononuclear cells (PBMCs), exhibiting IC_{50} values of 2.9, 2.9 and 11.0 μ M vs. 125.6, 130.0 and > 100 μ M for leflunomide, respectively. Antiinflammatory activity was demonstrated *in vivo* in the rat adjuvant-induced arthritis model following p.o. administration. Within this series of A-771726 analogues, the following are also included:



Compound	R1	Formula
276640	4-CF ₃ -PhNHCOC[=CH(OH)Me]	C ₁₉ H ₁₄ F ₆ N ₂ O ₃
276641	4-OH-2-oxo-3-THF	C ₁₂ H ₁₀ F ₃ NO ₄
276643	2-OH-6-oxo-cyclohexyl	C ₁₄ H ₁₄ F ₃ NO ₃
276644	2-OH-Ph	C ₁₄ H ₁₀ F ₃ NO ₂

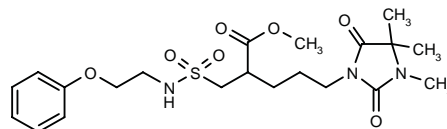
SOURCE – Italfarmaco.

REFERENCES

1. Bertolini, G. et al. (Italfarmaco SpA) *Analogues of the active metabolite of leflunomide*. US 5905090.

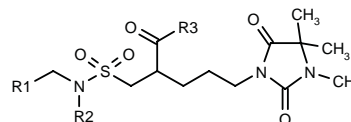
276907

2-[*N*-(2-Phenoxyethyl)sulfamoylmethyl]-5-(3,4,4-trimethyl-2,5-dioximidazolidin-1-yl)pentanoic acid methyl ester



C₂₁ H₃₁ N₃ O₇ S; Mol wt: 469.5559

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysin, collagenases and gelatinases, as well as of the production of tumor necrosis factor (TNF), with potential in the treatment of arthritis, osteoporosis, periodontal disease, asthma, adult respiratory distress syndrome, cancer, Alzheimer's disease, multiple sclerosis, ulcerative colitis, fever, cardiovascular disorders, cachexia, acute infection, HIV infection, shock states, graft-versus-host reaction, autoimmune disorders and reperfusion injury. Other specifically claimed compounds from this series of hydroxamic and carboxylic acid derivatives include the following:



Compound	R1	R2	R3	Formula
276908	CH ₂ OPh	Me	OMe	C ₂₂ H ₃₃ N ₃ O ₅ S
276910	4-Cl-PhOCH ₂	Me	OMe	C ₂₂ H ₃₂ ClN ₃ O ₅ S
276911	2-benzofuryl	Me	t-BuO	C ₂₆ H ₃₇ N ₃ O ₅ S
276912	CH ₂ OPh	H	OH	C ₂₀ H ₂₉ N ₃ O ₅ S
276913	2-benzofuryl	Me	OH	C ₂₂ H ₂₉ N ₃ O ₅ S
276914	CH ₂ OPh	H	NHOH	C ₂₀ H ₃₀ N ₄ O ₅ S

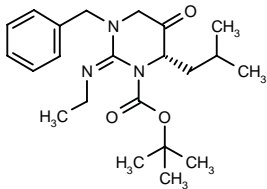
SOURCE – Darwin Discovery.

REFERENCES

1. Baxter, A.D. et al. (Darwin Discovery Ltd.) *Hydroxamic and carboxylic acid derivs. having MMP and TNF inhibitory activity*. WO 9924399.

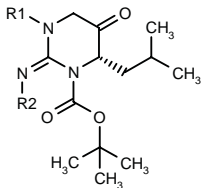
276915

3-Benzyl-2-(ethylimino)-6(*S*)-isobutyl-5-oxohexahydro-pyrimidine-1-carboxylic acid *tert*-butyl ester



C22 H33 N3 O3; Mol wt: 387.5207

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysin, collagenases and gelatinases, as well as of the production of tumor necrosis factor (TNF), with potential in the treatment of arthritis, osteoporosis, periodontal disease, asthma, adult respiratory distress syndrome, cancer, Alzheimer’s disease, multiple sclerosis, ulcerative colitis, fever, cardiovascular disorders, cachexia, acute infection, HIV infection, shock states, graft-versus-host reaction, autoimmune disorders and reperfusion injury. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Formula
276916	i-Pr	cyclohexyl	C ₂₂ H ₃₀ N ₃ O ₃
276917	(CH ₂) ₃ Ph	CH(Me)Ph	C ₃₀ H ₄₁ N ₃ O ₃
276918	1-cyclohexenyl-CH ₂ CH ₂	C ₅ H ₁₁	C ₂₆ H ₄₅ N ₃ O ₃
276919	(CH ₂) ₃ Ph	Et	C ₂₄ H ₃₇ N ₃ O ₃
276920	(CH ₂) ₃ Ph	1-Naph-CH(Me)	C ₃₄ H ₄₃ N ₃ O ₃
276921	(CH ₂) ₃ Ph	allyl	C ₂₅ H ₃₇ N ₃ O ₃

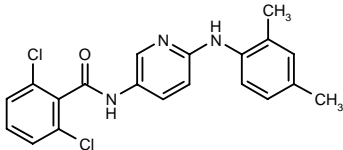
SOURCE – Darwin Discovery.

REFERENCES

1. Baxter, A.D. et al. (Darwin Discovery Ltd.) *Heterocyclic cpds. having MMP and TNF inhibitory activity*. WO 9924408.

276922

2,6-Dichloro-*N*-[6-(2,4-dimethylphenylamino)pyridin-3-yl]benzamide



C20 H17 Cl2 N3 O; Mol wt: 386.2803

ACTION – Agent for the treatment of cytokine-mediated disorders such as inflammation, cancer, diabetes and pain that acts by inhibiting the production of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), IL-1 β , IL-6 and/or IL-8; in addition, compound was also shown to inhibit cyclooxygenase. A representative compound from a series of substituted pyridine derivatives.

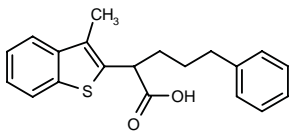
SOURCE – Amgen.

REFERENCES

1. Mantlo, N.B. et al. (Amgen Inc.) *Substd. pyridine cpds. as anti-inflammatory agents*. WO 9924404.

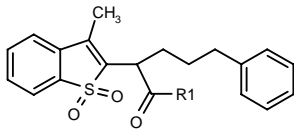
276923

2-(3-Methylbenzo[*b*]thiophen-2-yl)-5-phenylpentanoic acid

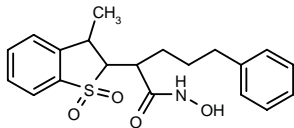


C20 H20 O2 S; Mol wt: 324.4420

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysins, collagenases and gelatinases, as well as of the production of tumor necrosis factor (TNF), with potential in the treatment of arthritis, osteoporosis, periodontal disease, asthma, adult respiratory distress syndrome, cancer, Alzheimer’s disease, multiple sclerosis, ulcerative colitis, fever, cardiovascular disorders, cachexia, acute infection, HIV infection, shock states, graft-versus-host reaction, autoimmune disorders and reperfusion injury. Other specifically claimed compounds from this series of hydroxamic and carboxylic acid derivatives include the following:



Compound	R1	Formula
276924	OH	C ₂₀ H ₂₀ O ₄ S
276925	NHOH	C ₂₀ H ₂₁ NO ₄ S



276926: C20 H23 N O4 S

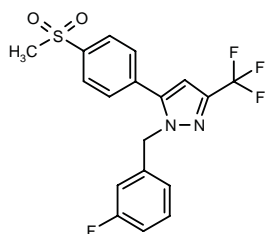
SOURCE – Darwin Discovery.

REFERENCES

1. Baxter, A.D. et al. (Darwin Discovery Ltd.) *Hydroxamic and carboxylic acid derivs. having MMP and TNF inhibitory activity*. WO 9924419.

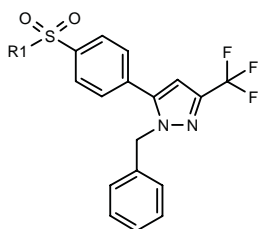
276946

1-(3-Fluorobenzyl)-5-(4-methylsulfonylphenyl)-3-trifluoromethyl-1*H*-pyrazole



C₁₈ H₁₄ F₄ N₂ O₂ S; Mol wt: 398.3786

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2) proven active *in vivo* in the adjuvant-induced arthritis model in the rat (> 60% inhibition at 1.0 mg/kg/day p.o. x 23 days). Other compounds from this series of 5-arylpyrazole derivatives include the following:



Compound	R1	Formula
276947	Me	C ₁₈ H ₁₅ F ₃ N ₂ O ₂ S
276948	NH ₂	C ₁₇ H ₁₄ F ₃ N ₃ O ₂ S

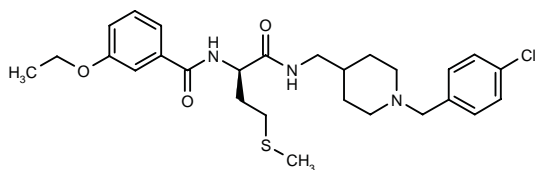
SOURCE – Fujisawa.

REFERENCES

1. Nakamura, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *5-Arylpyrazole cpds.* WO 9925695.

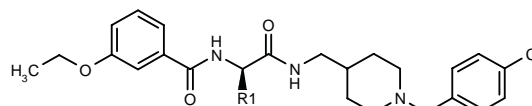
276992

*N*¹-[1-(4-Chlorobenzyl)piperidin-4-ylmethyl]-*N*²-(3-ethoxybenzoyl)-D-methioninamide

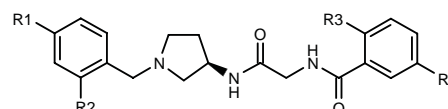


C₂₇ H₃₆ Cl N₃ O₃ S; Mol wt: 518.1184

ACTION – Agent for the treatment of rheumatoid arthritis, atherosclerosis, psoriasis, asthma, ulcerative colitis, nephritis and other disorders characterized by tissue infiltration of monocytes and lymphocytes, a chemokine receptor antagonist that inhibits the action of chemokines such as macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1) on target cells. *In vitro*, compound was shown to inhibit the binding of human MIP-1α to human monocytic leukemia THP-1 cells, producing > 80% inhibition at 2 μM. Other exemplified compounds within this broad series of cyclic amine derivatives include the following:



Compound	R1	Formula
276993	Pr	C ₂₇ H ₃₆ ClN ₃ O ₃
276994	Ph	C ₃₀ H ₃₄ ClN ₃ O ₃
276995	CH(Me)OCH ₂ Ph	C ₃₃ H ₄₀ ClN ₃ O ₄
276996	CH ₂ CH ₂ CO ₂ Me	C ₂₈ H ₃₆ ClN ₃ O ₅



Compound	R1	R2	R3	R4	Formula
276997	NHAc	H	H	CF ₃	C ₂₃ H ₂₅ F ₃ N ₄ O ₃
276998	Me	Me	NH ₂	I	C ₂₂ H ₂₇ IN ₄ O ₂
276999	Me	Me	NH ₂	NO ₂	C ₂₂ H ₂₇ N ₅ O ₄

SOURCES – CombiChem; Teijin.

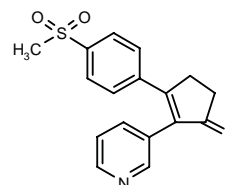
REFERENCES

1. Beckett, R.P. et al. (Teijin Ltd.;CombiChem, Inc.) *Cyclic amine derivatives and their use as drugs.* WO 9925686.

L-784506*

258598

3-[4-(Methylsulfonyl)phenyl]-2-(3-pyridyl)-2-cyclopenten-1-one



C₁₇ H₁₅ N O₃ S; Mol wt: 313.3755

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.17 and 0.64 μM in CHO cells and human whole blood, respectively) with more than 200-fold selectivity over COX-1 (IC₅₀ = 34 and 73 μM in U937 microsomes and human whole blood, respectively). In rats, compound showed excellent oral bioavailability (84%) and a long half-life (2 h). L-784506 was effective in standard rat models of inflammation (carrageenan-induced paw edema; ED₅₀ = 1.7 mg/kg p.o.), pyresis (ED₅₀ = 0.7 mg/kg p.o.) and mechanical hyperalgesia (ED₅₀ = 0.7 mg/kg p.o.) and in a model of chronic inflammation (adjuvant-induced arthritis; ED₅₀ = 0.6 mg/kg p.o.). It also exhibited a good safety profile, with a much reduced risk of gastrointestinal toxicity compared to conventional NSAIDs.

SOURCE – Merck Frosst.

REFERENCES

1. Black, C. et al. (Merck Frosst Canada Inc.) *3,4-Diaryl-2-hydroxy-2,5-dihydrofurans as prodrugs to Cox-2 inhibitors.* EP 904269, JP 99500748, US 5698584, WO 9716435.

2. Black, C. et al. (Merck Frosst Canada Inc.) *Pyridinyl-2-cyclopenten-1-ones as selective cyclooxygenase-2 inhibitors.* EP 900201, US 5922742, WO 9740012.

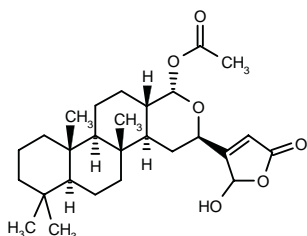
3. Black, W.C. et al. *2,3-Diaryl cyclopentenones as orally active, highly selective cyclooxygenase-2 inhibitors*. J Med Chem 1999, 42(7): 1274.

*Identified compound **258598** (see **257715**) Drug Data Report 1998, 020(02): 0161.

PETROSASPONGIOLIDE M

275311

4-[(1*S*,3*R*,4*aR*,4*bS*,6*aS*,10*aS*,10*bS*,12*aS*)-1-Acetoxy-4*b*,7,7,10*a*-tetramethylhexadecahydro-1*H*-phenanthro[2,1-*c*]pyran-3-yl]-5-hydroxyfuran-2(5*H*)-one



C27 H40 O6; Mol wt: 460.6070

ACTION – Orally active antiinflammatory agent, a metabolite extracted from the Caledonian marine sponge *Petrosaspongia nigra* with potent phospholipase A₂ (PLA₂)-inhibitory activity and selectivity for secretory over cytosolic PLA₂; compound exhibited potency similar to that of manoolide against human synovial PLA₂ (group II; IC₅₀ = 4.3 and 3.9 μM, respectively), but it exhibited little or no activity against group I PLA₂ (porcine pancreatic and *Naja naja* PLA₂). It showed antiinflammatory activity *in vivo* in the carrageenan-induced paw edema model in mice, in the air pouch model in rats and mice, and it was also effective (20 mg/kg p.o.) against chronic inflammation in adjuvant-induced arthritis in rats; in the latter model, it reduced serum LTB₄ levels and PGE₂ levels in the paw homogenates, whereas it did not affect serum or stomach PGE₂ levels or serum TxB₂ levels.

SOURCES – Università degli Studi di Napoli, Napoli (IT); Universidad de Valencia, Valencia (ES).

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- Randazzo, A. et al. *Petrosaspongiolides M-R: New potent and sselective phospholipase A2 inhibitors from the New Caledonian marine sponge Petrosaspongia nigra*. J Nat Prod 1998, 61(5): 571.

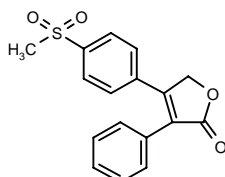
ROFECOXIB+

Prop INN

221147

4-[4-(Methylsulfonyl)phenyl]-3-phenylfuran-2(5*H*)-one

MK-0966
MK-966



C17 H14 O4 S; Mol wt: 314.3596

ACTION – Nonsteroidal antiinflammatory agent with analgesic activity, a specific inhibitor of cyclooxygenase type 2 (COX-2).

INDICATION – For the relief of pain, the treatment of primary dysmenorrhea and the acute and chronic treatment of the signs and symptoms of osteoarthritis.

PRESENTATION – Tablets, 12.5 and 25 mg.

PROPRIETARY NAME – Vioxx (MX, US).

SOURCE – Merck & Co.

RECENT REFERENCES

- Acevedo, E. et al. *Rofecoxib, a COX-2 specific inhibitor (C-2 SI), had clinical efficacy comparable to diclofenac in the treatment of knee and hip osteoarthritis (OA) in a one-year controlled clinical trial*. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 858.
- Bolognese, J. et al. *Precision of composite measures of osteoarthritis efficacy compared with that of individual endpoints*. 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 1974.
- Brown, J. et al. *MK-0966 50 mg versus ibuprofen 400 mg in post surgical dental pain*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PI-4.
- Brown, J. et al. *The COX-2 specific inhibitor, MK-0966, is effective in the treatment of primary dysmenorrhea*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PI-5.
- Bukasa, A. et al. *Selectivities of non-steroidal anti-inflammatory drugs as inhibitors of purified ovine COX-1 and COX-2: Effects of human plasma*. Br J Pharmacol 1999, 126(Suppl.): Abst 156P.
- Cannon, G. et al. *MK-0966, a specific COX-2 inhibitor, has clinical efficacy comparable to diclofenac in the treatment of knee and hip osteoarthritis (OA) in a 26-week controlled clinical trial*. 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 983.
- Cryer, B. et al. *In vivo effects of rofecoxib, a new cyclooxygenase (COX)-2 inhibitor, on gastric mucosal prostaglandin (PG) and serum thromboxane B2 (TXB2) synthesis in healthy humans*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 2268.
- Chan, C.-C. et al. *Preclinical biological profile of rofecoxib (Vioxx™), MK-0966): A potent, orally active and highly selective COX-2 inhibitor*. Mediators Inflamm 1999, 8(Suppl. 1): Abst P-14-1.
- Daniels, S. et al. *Dose ranging trial of the effect of MK-966 in primary dysmenorrhea*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PI-6.
- Day, R. et al. *Rofecoxib, a COX-2 specific inhibitor (C-2 SI), had clinical efficacy comparable to ibuprofen in the treatment of knee and hip osteoarthritis (OA) in a 6-week controlled clinical trial*. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 860.
- Ehrich, E. et al. *Improvements in SF-36 mental health domains with treatment of OA: A result of decreased pain and disability or independent mechanisms?* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 1134.
- Ford-Hutchinson, T. *New highly selective COX-2 inhibitors*. William Harvey Res Conf. Clin Benefits Sel COX-2 Inhib (April 22-24, Boston) 1998, 25.
- Fricke, J. et al. *MK-966 versus naproxen sodium 550 mg in postsurgical dental pain*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PI-7.
- Greenberg, H.E. et al. *MK-0966, a cyclooxygenase (COX-2) specific inhibitor, had no effect on the anti-platelet activity of low-dose aspirin (ASA) measured by serum thromboxane B2 (TXB2) production and platelet aggregation*. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PII-66.
- Hawkey, C. et al. *Treatment of osteoarthritis with rofecoxib, a cyclooxygenase-2 (COX-2) specific inhibitor, was associated with a lower incidence of gastroduodenal ulcers compared to ibuprofen and was comparable to placebo treatment*. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 861.
- Laine, L. et al. *Effect on the COX-2 specific inhibitor (C-2SI) rofecoxib on ulcer formation: A double-blind comparison with ibuprofen and placebo*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 1204.
- Langman, M. et al. *Lower incidence of clinically evident upper-GI perforations, ulcers and bleeds in patients treated with rofecoxib vs. nonspecific cyclooxygenase inhibitors*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 2269.

18. Mehlisch, D.R. et al. *Ex vivo* assay of COX-2 inhibition predicts analgesic efficacy in post-surgical dental pain with MK-966. Clin Pharmacol Ther 1998, 63(2): Abst P1-8.

19. Prasit, P. et al. The discovery of rofecoxib, [MK 966, Vioxx®, 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone], an orally active cyclooxygenase-2 inhibitor. Bioorg Med Chem Lett 1999, 9(13): 1773.

20. Saag, K. et al. MK-0966, a specific COX-2 inhibitor, has clinical efficacy comparable to ibuprofen in the treatment of knee and hip osteoarthritis (OA) in a 6-week controlled clinical trial. 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 984.

21. Schwartz, J. et al. Antipyretic activity of a selective cyclooxygenase (COX)-2 inhibitor MK-0966. Clin Pharmacol Ther 1998, 63(2): Abst P1-123.

22. Schwartz, J. et al. Influence of antacids on the bioavailability (F) of a specific cyclooxygenase (COX)-2 inhibitor, MK-0966 (M) in the elderly. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst P11-104.

23. Schwartz, J.I. et al. Comparative inhibitory activity of rofecoxib (MK-0966, Vioxx™), meloxicam, diclofenac, ibuprofen and naproxen on COX-2 vs COX-1 in healthy female volunteers. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 857.

24. Schwartz, J.I. et al. Influence of a selective cyclooxygenase-2 (COX-2) inhibitor, rofecoxib (MK-0966, Vioxx™), on prednisone and prednisolone plasma concentrations. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 856.

25. Schwartz, J.I. et al. Influence of the selective cyclooxygenase-2 inhibitor, MK-0966 [MK], on cytochrome P450 [CYP] activity. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.8.

26. Schwartz, J.I. et al. Influence of the selective cyclooxygenase-2 inhibitor, MK-0966 [MK], on digoxin [DG] serum concentrations. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.9.

27. Siegl, P.K.S. et al. Effect of age on renal responses to COX-2 inhibitors, rofecoxib (VIOXX™, MK-0966), celecoxib and meloxicam in conscious dogs. Am J Hypertens 1999, 12(4, Part 2): 58A.

28. Truitt, K. et al. Rofecoxib, a COX-2 specific inhibitor, had clinical efficacy and overall safety in treating osteoarthritis patients aged 80 years and older. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 859.

29. Van Hecken, A. et al. Demonstration of specific COX-2 inhibition by MK-966 in humans with supratherapeutic doses. 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst P11-69.

30. Watson, D.J. et al. Lower incidence of GI-related discontinuations and "NSAID-type" symptoms in patients treated with rofecoxib vs. nonspecific cyclooxygenase inhibitors. 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 863.

31. Zeng, Q. et al. Comparison of several composite endpoints in the assessment of MK-0966 efficacy in rheumatoid arthritis. 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 1045.

32. COX-2-specific inhibitor from Merck filed for approval with FDA. DailyDrugNews.com (Daily Essentials) 1998, Nov 24.

33. FDA advisory committee votes in favor of approval for Vioxx. DailyDrugNews.com (Daily Essentials) 1999, April 21.

34. FDA approves Vioxx for osteoarthritis, acute pain and menstrual pain. DailyDrugNews.com (Daily Essentials) 1999, May 25.

35. Health Canada grants priority review status for rofecoxib. DailyDrugNews.com (Daily Essentials) 1999, April 20.

36. Merck presents clinical data on COX-2 inhibitor at FASEB 98. DailyDrugNews.com (Daily Essentials) 1998, April 28.

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38. Proposed international nonproprietary names (Prop. INN): List 80. WHO Drug Inf 1998, 12(4): 274.

39. Rofecoxib up for advisory committee review this spring. DailyDrugNews.com (Daily Essentials) 1999, Feb 26.

40. U.K. is first European country to approve Vioxx for marketing; U.S. introduction announced. DailyDrugNews.com (Daily Essentials) 1999, June 11.

MONOGRAPH – Sorbera, L.A. et al. Rofecoxib. Drugs Fut 1998, 023(12): 1287.

*Drug Data Rep 1999, 021(01): 0072.

IMMUNOMODULATING AGENTS

276413

Recombinant high-molecular-weight protein isolated from Chlamydia spp. with an apparent molecular weight of about 105-115 kD

ACTION – Recombinant high-molecular-weight protein from Chlamydia trachomatis for use in the treatment or prevention of Chlamydia infections in mammals, as well as for inducing immune responses to Chlamydia, as demonstrated in several tests. In addition, it was shown to be effective in protecting mice against C. trachomatis-induced salpingitis and infertility.

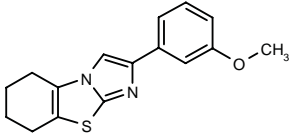
SOURCE – Antex Biologics.

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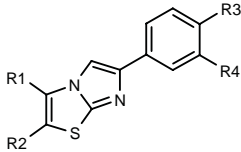
276625

2-(3-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[2,1-b]-benzothiazole



C16 H16 N2 O S; Mol wt: 284.3814

ACTION – Agent for the treatment or prevention of allergic disorders, autoimmune diseases, parasitic, viral or bacterial infections, cancer, graft-versus-host disease and AIDS that acts by inhibiting STAT-6 activation, as demonstrated in a luciferase assay using L929 cells transfected with the STAT-6 reporter gene. A representative compound from a series of imidazo[2,1-b]-[1,3]thiazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
276626	H	H	Ph	H	C ₁₇ H ₁₂ N ₂ S
276627	H	H	Cl	H	C ₁₁ H ₇ ClN ₂ S
276628	H	H	Br	H	C ₁₁ H ₇ BrN ₂ S
276629	H	H	-CH=CHCH=CH-		C ₁₅ H ₁₀ N ₂ S
276630		-CH=CHCH=CH-	F	H	C ₁₅ H ₉ FN ₂ S
276631		-CH=CHCH=CH-	Cl	H	C ₁₅ H ₉ ClN ₂ S
276632		-CH=CHCH=CH-	Br	H	C ₁₅ H ₉ BrN ₂ S
276633		-CH=CHCH=CH-	H	OMe	C ₁₆ H ₁₂ N ₂ OS
276634		-CH=CHCH=CH-	-CH=CHCH=CH-		C ₁₉ H ₁₂ N ₂ S
276635		-(CH ₂) ₄ -	F	H	C ₁₅ H ₁₃ FN ₂ S
276636		-(CH ₂) ₄ -	Cl	H	C ₁₅ H ₁₃ ClN ₂ S
276637		-(CH ₂) ₄ -	Br	H	C ₁₅ H ₁₃ BrN ₂ S

18. Mehlisch, D.R. et al. *Ex vivo* assay of COX-2 inhibition predicts analgesic efficacy in post-surgical dental pain with MK-966. Clin Pharmacol Ther 1998, 63(2): Abst P1-8.

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*Drug Data Rep 1999, 021(01): 0072.

IMMUNOMODULATING AGENTS

276413

Recombinant high-molecular-weight protein isolated from Chlamydia spp. with an apparent molecular weight of about 105-115 kD

ACTION – Recombinant high-molecular-weight protein from Chlamydia trachomatis for use in the treatment or prevention of Chlamydia infections in mammals, as well as for inducing immune responses to Chlamydia, as demonstrated in several tests. In addition, it was shown to be effective in protecting mice against C. trachomatis-induced salpingitis and infertility.

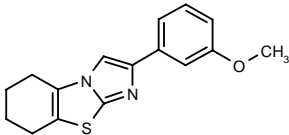
SOURCE – Antex Biologics.

REFERENCES

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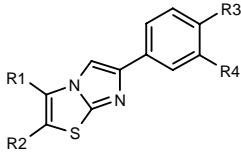
276625

2-(3-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[2,1-b]-benzothiazole



C16 H16 N2 O S; Mol wt: 284.3814

ACTION – Agent for the treatment or prevention of allergic disorders, autoimmune diseases, parasitic, viral or bacterial infections, cancer, graft-versus-host disease and AIDS that acts by inhibiting STAT-6 activation, as demonstrated in a luciferase assay using L929 cells transfected with the STAT-6 reporter gene. A representative compound from a series of imidazo[2,1-b]-[1,3]thiazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
276626	H	H	Ph	H	C ₁₇ H ₁₂ N ₂ S
276627	H	H	Cl	H	C ₁₁ H ₇ ClN ₂ S
276628	H	H	Br	H	C ₁₁ H ₇ BrN ₂ S
276629	H	H	-CH=CHCH=CH-		C ₁₅ H ₁₀ N ₂ S
276630		-CH=CHCH=CH-	F	H	C ₁₅ H ₉ FN ₂ S
276631		-CH=CHCH=CH-	Cl	H	C ₁₅ H ₉ ClN ₂ S
276632		-CH=CHCH=CH-	Br	H	C ₁₅ H ₉ BrN ₂ S
276633		-CH=CHCH=CH-	H	OMe	C ₁₆ H ₁₂ N ₂ OS
276634		-CH=CHCH=CH-	-CH=CHCH=CH-		C ₁₉ H ₁₂ N ₂ S
276635		-(CH ₂) ₄ -	F	H	C ₁₅ H ₁₃ FN ₂ S
276636		-(CH ₂) ₄ -	Cl	H	C ₁₅ H ₁₃ ClN ₂ S
276637		-(CH ₂) ₄ -	Br	H	C ₁₅ H ₁₃ BrN ₂ S

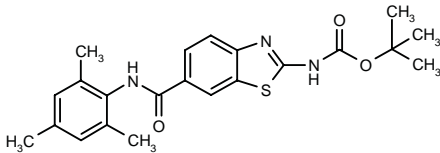
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REFERENCES

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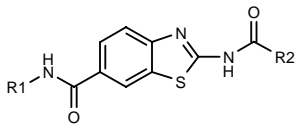
276865

N-[6-[N-(2,4,6-Trimethylphenyl)carbamoyl]benzothiazol-2-yl]carbamic acid *tert*-butyl ester



C22 H25 N3 O3 S; Mol wt: 411.5235

ACTION – An inhibitor of protein tyrosine kinases, particularly Lck tyrosine kinase, with potential in the treatment of T-cell-mediated disorders such as rheumatoid arthritis, multiple sclerosis, lupus, transplant rejection and delayed-type hypersensitivity (DTH) reactions. Other specifically claimed compounds within this series of benzothiazole derivatives include the following:



Compound	R1	R2	Formula
276866	2,4,6-(Me)3-Ph	N(i-Pr)2	C ₂₄ H ₃₀ N ₄ O ₂ S
276867	2,4,6-(Me)3-Ph	1-(CH ₂ OH)- -cyclopentyl-NH	C ₂₄ H ₂₈ N ₄ O ₃ S
276868	2,4,6-(Me)3-Ph	3-MeO-PhNH	C ₂₅ H ₂₄ N ₄ O ₃ S
276869	2,4,6-(Me)3-Ph	2-MeO-PhCH ₂ CH ₂	C ₂₇ H ₂₇ N ₃ O ₃ S
276870	3-OH-2-Naph	t-BuO	C ₂₃ H ₂₁ N ₃ O ₄ S
276871	2,4,6-(Me)3-Ph	NHMe	C ₁₉ H ₂₀ N ₄ O ₂ S
276872	2-Cl-6-Me-Ph	4-Me-cyclohexyl-NH	C ₂₃ H ₂₅ ClN ₄ O ₂ S
276873	2-Cl-6-Me-Ph	CH ₂ CH ₂ Ph	C ₂₄ H ₂₀ ClN ₃ O ₂ S
276874	2-Cl-6-Me-Ph	2-(PhCH ₂)- -cyclopropyl	C ₂₆ H ₂₂ ClN ₃ O ₂ S
276875	2,6-(Me)2-Ph	1,3-benzodioxol-5-yl- -CH ₂ CH ₂	C ₂₆ H ₂₃ N ₃ O ₄ S
276876	2,4,6-(Me)3-Ph	2-CHO-cyclopropyl	C ₂₂ H ₂₁ N ₃ O ₃ S
276877	2-Cl-6-Me-Ph	3-MeO-PhCH ₂ CH ₂ NH	C ₂₅ H ₂₃ ClN ₄ O ₃ S

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Das, J. et al. (Bristol-Myers Squibb Co.) *Benzothiazole protein tyrosine kinase inhibitors*. WO 9924035.

276937

Auxotrophic attenuated strains of *Listeria*

ACTION – Vaccine vector comprising auxotrophic attenuated strains of *Listeria* expressing heterologous antigens. The auxotrophic attenuated strain comprises a mutation in at least one gene whose protein product is essential for the growth of *Listeria* and the *Listeria* is preferably *Listeria monocytogenes*. The heterologous antigen may be an HIV-1 antigen or tumor or tumor-related antigens. The attenuated auxotrophic strains of *Listeria* produce a host cytotoxic T-cell (CTL) response directed against *Listeria* and may thus be used as a vaccine for the treatment and/or prevention of *Listeria* infection, as well as for other infections and cancer.

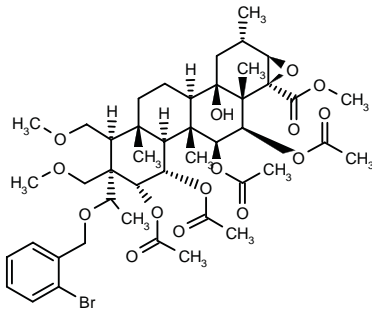
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Frankel, F.R. and Portnoy, D.A. (University of Pennsylvania) *Bacterial vaccines comprising auxotrophic, attenuated strains of Listeria expressing heterologous antigens*. WO 9925376.

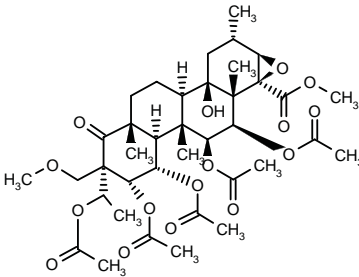
276938

(1*aR*,2*S*,3*aR*,3*bR*,5*aS*,6*S*,7*R*,8*R*,9*S*,9*aS*,9*bR*,10*S*,11*R*,11*aR*,11*bS*)-8,9,10,11-Tetra(acetoxy)-7-[1-(2-bromo-benzyloxy)ethyl]-3*a*-hydroxy-2,5*a*,9*b*,11*a*-tetramethyl-6,7-(dimethoxymethyl)perhydrochryseno[1,2-*b*]oxirene-11*b*-carboxylic acid methyl ester



C45 H63 Br O15; Mol wt: 923.8817

ACTION – Immunosuppressive agent proven to inhibit the voltage-dependent potassium channel Kv1.3 found on human T-lymphocytes, and to inhibit IL-2 production by T-cells and T-cell proliferation. Potentially useful in the treatment of autoimmune diseases and for the prevention of transplant rejection. Another specifically claimed tetracyclic triterpene is:



276939: C38 H54 O16

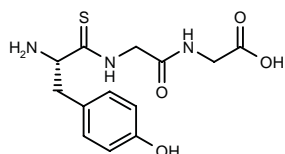
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Immunosuppressant tetracyclic triterpenes*. WO 9925703.

277084

L-Thiotyrosyl-glycyl-glycine



C13 H17 N3 O4 S; Mol wt: 311.3603

ACTION – Immunostimulant, an analogue of IMREG-1⁺ with improved stability, proven to induce weak stimulation of cytotoxic T-lymphocytes (CTLs) *in vitro* and to weakly induce T- and B-cell proliferation compared to IL-2, but to produce a significant increase in activated CTLs, NK cells and B-cells in the spleen of mice treated i.p. for 4 consecutive days at doses of 50-125 mg/kg. Potentially useful for the treatment of diseases where CTLs and NK cells play an important role such as cancer and viral infections, or as a vaccine adjuvant.

SOURCE – BioChem Pharma.

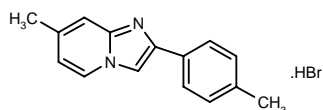
REFERENCES

1. Zackarie, B. et al. *Thioamides: Synthesis, stability, and immunological activities of thioanalogues of imreg. Preparation Of new thioacylating agents using fluorobenzimidazolone derivatives*. J Med Chem 1999, 42(11): 2046.

*Drug Data Rep 1985, 007(11): 0797.

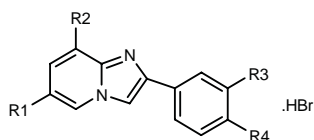
277273

7-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine hydrobromide



C15 H14 N2 . HBr; Mol wt: 303.2015

ACTION – Agent for the treatment of allergic disorders, autoimmune diseases, parasitic, viral and bacterial infections, cancer, graft-versus-host disease and AIDS, a STAT-6 activation inhibitor. Other compounds from this series of imidazo[1,2-a]pyridine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
277274	H	H	-CH=CHCH=CH-		C ₁₇ H ₁₂ N ₂ .HBr
277275	Br	Br	H	Me	C ₁₄ H ₁₀ N ₂ .HBr
277276	Cl	H	H	Me	C ₁₄ H ₁₁ ClN ₂ .HBr
277277	H	H	Cl	Cl	C ₁₃ H ₈ Cl ₂ N ₂ .HBr
277347	Me	H	H	Me	C ₁₅ H ₁₄ N ₂ .HBr

Compound	R1	R2	R3	R4	Formula
277349	CF ₃	H	H	Me	C ₁₅ H ₁₁ F ₃ N ₂ .HBr
277350	H	H	H	Ph	C ₁₉ H ₁₄ N ₂ .HBr

SOURCE – Sumitomo Pharmaceuticals.

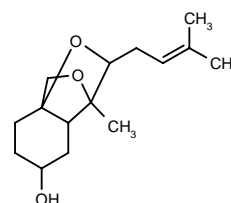
REFERENCES

1. Inoue, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Stat 6 activation inhibitors*. JP 99116481.

AM-6898E

277222

7-Methyl-11-(3-methylbut-2-enyl)-8,10-dioxatricyclo-[5.2.2.0^{1,6}]undecan-4-ol



C15 H24 O3; Mol wt: 252.3516

ACTION – Inhibitor of IgE antibody production isolated from *Pseudallescheria* sp. M6898 (FERM BP-5543) and shown to potently inhibit IgE antibody production in stimulated murine spleen cells (IC₅₀ = 0.009 µg/ml), whereas it was devoid of cytotoxicity in P388D1 cells (IC₅₀ > 50 µg/ml). Potentially useful for the treatment of immune disorders.

SOURCE – Asahi Chemical.

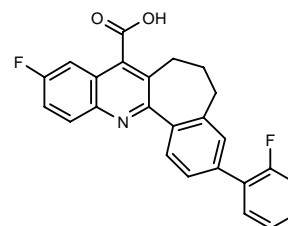
REFERENCES

1. Ishikawa, S. and Murofushi, S. (Asahi Chemical Industry Co., Ltd.) *Novel cpd. AM6898E and its preparation method*. JP 99116577.

KF-20444*

220318

10-Fluoro-3-(2-fluorophenyl)-6,7-dihydro-5H-benz[6,7]-cyclohepta[1,2-b]quinoline-8-carboxylic acid



C25 H17 F2 N O2; Mol wt: 401.4170

ACTION – Immunosuppressant, an inhibitor of dihydro-orotate dehydrogenase, a pyrimidine biosynthesis enzyme, with potent *in vitro* activity against TPN antibody production ($IC_{50} = 0.024 \mu M$) and approximately 30-fold more active than DuP-785. Compound inhibited the mixed lymphocyte reaction (MLR) proliferative response with an LC_{50} of $0.04 \mu M$. *In vivo*, compound (0.1-2 mg/kg) was effective in rats with heterotopic cardiac transplants, significantly prolonging graft survival, and it was more active and better tolerated than brequinar sodium. At a dose of 4 mg/kg compound showed gastrointestinal toxicity, causing death in 15% of treated animals.

SOURCE – Kyowa Hakko.

REFERENCES

1. Suzuki, F. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tetracyclic cpds.* US 5371225, WO 9322286.
2. Chujo, I. et al. *Synthetic study of novel immunosuppressant KF20444.* 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst ORGN 077.
3. Ito, H. et al. *Immunosuppressive activity of a novel compound KF20444.* Jpn J Transplant 1997, 32: Abst S-2-5.
4. Ito, T. et al. *Immunosuppressive effect on alloimmune responses of new immunosuppressant, KF20444.* Org Biol 1997, 4(2): 43.
5. Nakajima, H. et al. *Immunosuppressant effect of KF20444.* Jpn J Transplant 1996, 31: Abst 194.
6. Nakajima, H. et al. *Immunosuppressive action of KF20444, a novel immunosuppressive agent.* 17th Meet Jpn Inflamm Soc (July 11-12, Tokyo) 1996, Abst 104.
7. Nakajima, H. et al. *Immunosuppressive effect of new immunosuppressant, KF20444.* Org Biol 1997, 4(2): 49.
8. Nakasato, Y. et al. *A new immunosuppressant. Structure-activity relationships of novel tetracyclic heterocycles.* AFMC Int Med Chem Symp (Sept 3-8, Tokyo) 1995, Abst P1M019.
9. Nomura, M. et al. *Effect of a new immunosuppressive agent, KF20444 on rat cardiac transplantation.* 17th World Cong Transplant Soc (July 12-17, Montréal) 1998, Abst 1614.
10. Nomura, M. et al. *Effect of a new immunosuppressive agent, KF20444, in rat cardiac transplantation.* Transplant Proc 1999, 31(1-2): 1206.
11. Ohkawa, J. et al. *Inhibition of alloimmune response by KF20444, a novel immunosuppressant.* Jpn J Transplant 1996, 31: Abst 193.
12. Tamura, T. et al. *Anti-rheumatic action of KF-20444, a novel immunosuppressive agent.* 17th Meet Jpn Inflamm Soc (July 11-12, Tokyo) 1996, Abst 103.

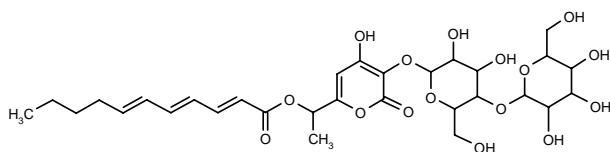
*Identified compound **220318** (see **218317**) Drug Data Report 1995, 017(05): 0475.

ONCOLYTIC DRUGS

ANTIMETABOLITES

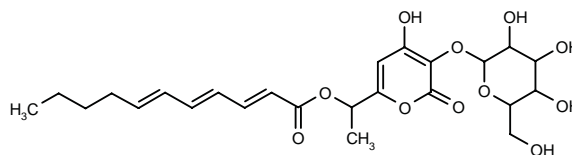
275520

2(E),4(E),6(E)-Undecatrienoic acid 1-[3-[4-O-(hexopyranosyl)hexopyranosyloxy]-4-hydroxy-2-oxo-2H-pyran-6-yl]ethyl ester



C30 H42 O16; Mol wt: 658.6458

ACTION – A novel α -pyrone that inhibits DNA ligase, potentially useful for the treatment of disorders associated with undesirable cell proliferation such as cancer and bacterial infections. Another specifically claimed compound is:



275521: C24 H32 O11

SOURCE – Millennium.

REFERENCES

1. Cohen, S. and Jiang, Z.-D. (Millennium Pharmaceuticals, Inc.) *α -Pyrone responsive states.* WO 9914211.

CYTARABINE LIPOSOME INJECTION

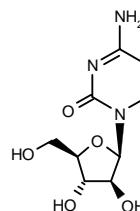
280234

Injectable sustained-release formulation of cytarabine using DepoFoam™ lipid-based drug delivery technology

Cytarabine

Rec INN; BAN; USAN

4-Amino-1- β -D-arabinofuranosyl-2(1H)-pyrimidinone



C9 H13 N3 O5; Mol wt: 243.2177

ACTION – Antineoplastic agent, a sustained-release, lipid-based formulation of cytarabine, an antimetabolite that appears to act mainly by inhibiting DNA polymerase following conversion to the triphosphate.

INDICATION – Intrathecal treatment of lymphomatous meningitis.

PRESENTATION – Single-use vials (5 ml), 50 mg (10 mg/ml).

PROPRIETARY NAME – DepoCyt (US).

SOURCES – DepoTech (now a part of Skye Pharma); marketed by Chiron.

REFERENCES

1. Braeckman, R. et al. *Pharmacokinetics (PK) of Depocyt(TM) after intrathecal administration for the treatment of leptomeningeal metastases (LM).* Proc Amer Soc Clin Oncol 1997, 16: Abst 810.
2. Cole, B.F. et al. *Quality-adjusted time without symptoms and toxicity (Q-TWIST) comparison of sustained release cytarabine (DepoCyt) vs. methotrexate (MTX) treatment for patients (pts) with carcinomatous meningitis.* Proc Amer Soc Clin Oncol 1998, 17: Abst 1560.
3. Chamberlain, M.C. et al. *Pharmacokinetics of intralumbar DTC-101 for the treatment of leptomeningeal metastases.* Arch Neurol 1995, 52(9): 912.

ACTION – Immunosuppressant, an inhibitor of dihydro-orotate dehydrogenase, a pyrimidine biosynthesis enzyme, with potent *in vitro* activity against TPN antibody production ($IC_{50} = 0.024 \mu M$) and approximately 30-fold more active than DuP-785. Compound inhibited the mixed lymphocyte reaction (MLR) proliferative response with an LC_{50} of $0.04 \mu M$. *In vivo*, compound (0.1-2 mg/kg) was effective in rats with heterotopic cardiac transplants, significantly prolonging graft survival, and it was more active and better tolerated than brequinar sodium. At a dose of 4 mg/kg compound showed gastrointestinal toxicity, causing death in 15% of treated animals.

SOURCE – Kyowa Hakko.

REFERENCES

1. Suzuki, F. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tetracyclic cpds.* US 5371225, WO 9322286.
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12. Tamura, T. et al. *Anti-rheumatic action of KF-20444, a novel immunosuppressive agent.* 17th Meet Jpn Inflamm Soc (July 11-12, Tokyo) 1996, Abst 103.

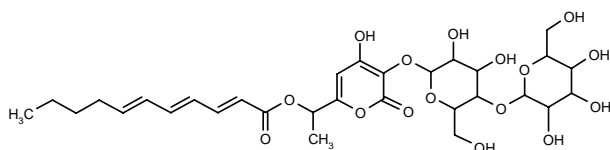
*Identified compound **220318** (see **218317**) Drug Data Report 1995, 017(05): 0475.

ONCOLYTIC DRUGS

ANTIMETABOLITES

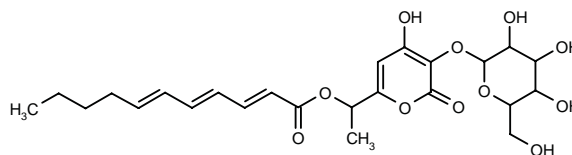
275520

2(E),4(E),6(E)-Undecatrienoic acid 1-[3-[4-O-(hexopyranosyl)hexopyranosyloxy]-4-hydroxy-2-oxo-2H-pyran-6-yl]ethyl ester



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275521: C24 H32 O11

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CYTARABINE LIPOSOME INJECTION

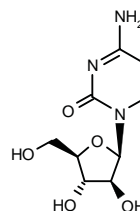
280234

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Rec INN; BAN; USAN

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3. Chamberlain, M.C. et al. *Pharmacokinetics of intralumbar DTC-101 for the treatment of leptomeningeal metastases.* Arch Neurol 1995, 52(9): 912.

4. Chamberlain, M.C. et al. *Treatment of leptomeningeal metastasis with intraventricular administration of depot cytarabine (DTC 101)*. Arch Neurol 1993, 50: 261.

5. Howell, S.B. et al. *A controlled trial of DepoCyt(TM) for the treatment of lymphomatous meningitis*. Proc Amer Soc Clin Oncol 1999, 18: Abst 34.

6. Jaeckle, K. et al. *Treatment of carcinomatous meningitis (CM) and lymphomatous meningitis (LM) with intra-CSF cytarabine sustained-release liposome injection (DepoCyt(TM)) vs. methotrexate (MTX) and ara-C*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 344.

7. Kim, S. *DepoFoam-mediated drug delivery into cerebrospinal fluid*. Methods Neurosci 1994, 118.

8. Kim, S. et al. *Extended CSF cytarabine exposure following intrathecal administration of DTC 101*. J Clin Oncol 1993, 11(11): 2186.

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11. Maria, B.L. et al. *Cost of treating leptomeningeal metastases with intrathecal Depofoam(TM) encapsulated cytarabine*. Proc Amer Soc Clin Oncol 1996, 15: Abst 305.

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13. *Chiron and DepoTech complete NDA for DepoCyt*. DailyDrugNews.com (Daily Essentials) 1997, May 6.

14. *Chiron and DepoTech report positive interim results in phase 3 trial of DepoCyt*. DepoTech Corp. Press Release 1995, Aug 16.

15. *DepoCyt FDA review period extended in order to review additional patient data*. DailyDrugNews.com (Daily Essentials) 1998, March 9.

16. *DepoCyt to be reviewed by FDA advisory committee this month*. DailyDrugNews.com (Daily Essentials) 1997, Nov 11.

17. *DepoTech and Chiron announce additional phase 3 clinical trial results for DepoCyt; New drug delivery technology enhances effect of cancer drug*. Chiron Corp. Press Release 1996, Oct 21.

18. *DepoTech and Chiron submit NDA for DepoCyt*. DailyDrugNews.com (Daily Essentials) 1998, Oct 13.

19. *DepoTech and Chiron to collaborate on delivery of cancer therapeutics using DepoFoam(TM) technology*. DepoTech Corp. Press Release 1994, April 11.

20. *DepoTech begins filing of new drug application for DepoCyt*. DepoTech Corp. Press Release 1996, Nov 25.

21. *DepoTech commences phase III trials of DTC 101 in Canada*. DepoTech Corp. Press Release 1994, Nov 3.

22. *DepoTech completes \$11 million private financing including \$2.5 million from Chiron Corporation*. DepoTech Corp. Press Release 1994, April 11.

23. *DepoTech completes \$6.1 million financing*. DepoTech Corp. Press Release 1994, Dec 27.

24. *DepoTech Corp. begins pediatric study of DepoCyt*. DepoTech Corp. Press Release 1997, Feb 26.

25. *DepoTech reacquires certain marketing rights to DepoCyt*. DailyDrugNews.com (Daily Essentials) 1997, June 9.

26. *DepoTech receives approvals for new pilot manufacturing plant*. DepoTech Corp. Press Release 1995, April 20.

27. *DepoTech seeks Canadian approval for DepoCyt*. DailyDrugNews.com (Daily Essentials) 1997, Sept 4.

28. *DepoTech withdraws MAA for Savedar for solid tumor indication*. DailyDrugNews.com (Daily Essentials) 1998, Oct 19.

29. *DepoTech: Q4 and year-end 1997 highlights*. DailyDrugNews.com (Daily Essentials) 1998, March 9.

30. *European filing announced for Savedar (DepoCyt)*. DailyDrugNews.com (Daily Essentials) 1998, Jan 21.

31. *FDA advisory committee issues positive statement on DepoCyt*. DailyDrugNews.com (Daily Essentials) 1998, Nov 18.

32. *FDA Advisory Committee does not recommend approval for DepoCyt*. DailyDrugNews.com (Daily Essentials) 1997, Dec 19.

33. *FDA approves DepoCyt for treatment of lymphomatous meningitis*. DailyDrugNews.com (Daily Essentials) 1999, April 6.

34. *FDA indicates approvability of DepoCyt for neoplastic meningitis from lymphomas*. DailyDrugNews.com (Daily Essentials) 1998, Sept 7.

35. *FDA Oncologic Drugs Advisory Committee meets for two days in November*. DailyDrugNews.com (Daily Essentials) 1998, Oct 30.

36. *FDA says DepoCyt is not approvable*. DailyDrugNews.com (Daily Essentials) 1998, May 28.

37. *Oncologic Drugs Advisory Committee meets next week*. DailyDrugNews.com (Daily Essentials) 1997, Dec 10.

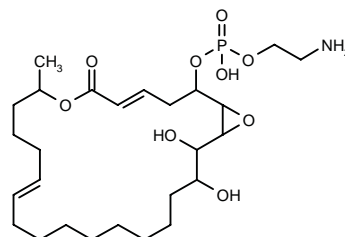
38. *SkyePharma announces U.S. launch of DepoCyt*. DailyDrugNews.com (Daily Essentials) 1999, , May 25.

ANTIBIOTICS AND ALKALOIDS

NF-06307

276623

5-[2-Aminoethoxy(hydroxy)phosphoryloxy]-6,7-epoxy-8,9-dihydroxy-2(*E*),18(*E*)-tetracosadieno-23-lactone



C₂₆ H₄₆ N O₉ P; Mol wt: 547.6214

ACTION – Physiologically active substance isolated from *Aspergillus* sp. NF06307 (FERM P-16064), proven to inhibit the proliferation of human ovarian cancer A2780 cells by over 90% at concentrations of 33.3-100 µg/ml.

SOURCE – Nippon Kayaku.

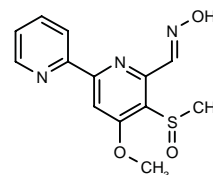
REFERENCES

1. Nishikiori, T. et al. (Nippon Kayaku Co., Ltd.) *Physiologically active substance NF06307, its preparation method and use*. JP 99106344.

PYRISULFOXIN A^{1,2}

276772

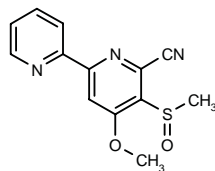
4-Methoxy-6-(2-pyridyl)-3-(methylsulfinyl)pyridine-2-carbaldehyde oxime



C₁₃ H₁₃ N₃ O₃ S; Mol wt: 291.3297

Colorless powder, m.p. 178-80 °C.

ACTION – Antineoplastic agent isolated from the culture broth of *Streptomyces californicus* BS-75, with potent *in vitro* cytotoxicity against murine leukemia P388 cells (IC_{50} = 0.1 μ g/ml). Another novel antibiotic from this source is:



Pyrifulfoxin B [276773]²: C₁₃ H₁₁ N₃ O₂ S

SOURCES – House Foods; University of Tokyo, Tokyo (JP).

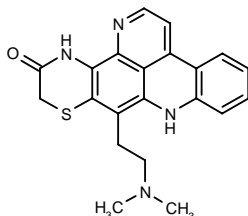
REFERENCES

1. Seto, H. et al. (House Foods Corp.) *2,2'-Bipyridine derivs., their preparation and antitumor agent containing them*. JP 97012550.
2. Tsuge, N. et al. *Novel antibiotics pyrifulfoxin A and B produced by Streptomyces californicus*. J Antibiot 1999, 52(5): 505.

SHERMILAMINE D

276604

9-[2-(Dimethylamino)ethyl]-11,13-dihydro-8*H*-pyrido[4,3,2-*mn*][1,4]thiazino[3,2-*b*]acridin-12-one



C₂₁ H₂₀ N₄ O S; Mol wt: 376.4820

ACTION – Cytotoxic pyridoacridine alkaloid isolated from the tunicate *Cystodytes violatinctus*, with IC_{50} values against murine leukemia P388, human lung carcinoma A-549, human colon carcinoma HT-29 and human melanoma MEL-28 cells of 1.33, 0.27, 2.66 and 0.53 μ M, respectively.

SOURCE – Instituto Biomar.

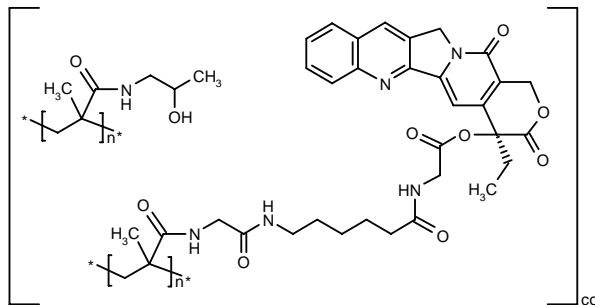
REFERENCES

1. Kashman, Y. et al. (Instituto Biomar SA) *Cytotoxic pyridoacridine alkaloids*. WO 9923099.

DNA-INTERCALATING DRUGS

276549

Copolymer of *N*-(2-hydroxypropyl)methacryloylamide and 20-*O*-[*N*-methacryloyl-glycyl-(6-aminohexanoyl)-glycyl]-camptothecin



((C₃₄ H₃₇ N₅ O₈)_n(C₇ H₁₃ N O₂)_n)_{co}

ACTION – Antineoplastic agent, a water-soluble polymeric conjugate of camptothecin with enhanced antitumor activity and decreased toxicity compared to the free drug, as demonstrated *in vivo* in nude mice bearing human colon carcinoma HT-29, human mammary carcinoma MX-1, human ovarian carcinoma A2780, human melanoma M14 and human non-small cell lung carcinoma A549 tumors following i.v. administration.

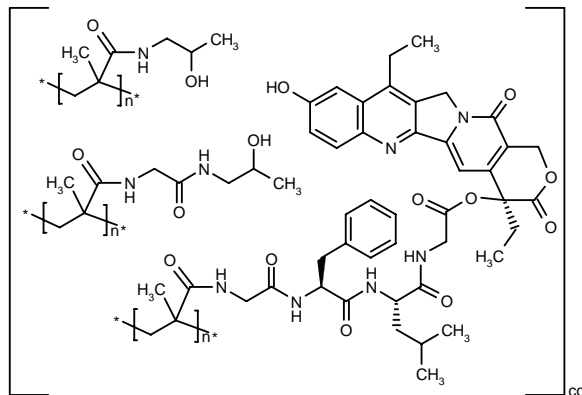
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Angelucci, F. et al. (Pharmacia & Upjohn SpA) *Polymeric derivs. of camptothecins*. WO 9917804.

276552

Copolymer of *N*-(2-hydroxypropyl)-2-methacrylamide, 7-ethyl-10-hydroxy-20-*O*-(*N*-methacryloyl-glycyl-L-phenylalanyl-L-leucyl-glycyl)camptothecin and *N*¹-(2-hydroxypropyl)-*N*²-(methacryloyl)glycinamide



((C₉ H₁₆ N₂ O₃)_n(C₄₅ H₅₀ N₆ O₁₀)_n(C₇ H₁₃ N O₂)_n)_{co}

ACTION – Antineoplastic agent, a water-soluble polymeric conjugate of 7-ethyl-10-hydroxycamptothecin with comparable antitumor activity and reduced toxicity compared to the free drug.

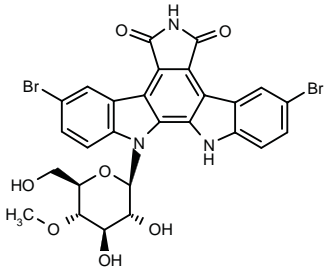
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Angelucci, F. et al. (Pharmacia & Upjohn SpA) *Bioactive derivs. of camptothecin*. WO 9917805.

277046

3,9-Dibromo-12-(4-*O*-methyl-β-*D*-glucopyranosyl)-6,7,12,13-tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C27 H21 Br2 N3 O7; Mol wt: 659.2849

Yellow solid, *m.p.* 270 °C.

ACTION – Antineoplastic and antimicrobial agent, a rebeccamycin derivative that acts as a potent and specific inhibitor of topoisomerase I (MIC = 0.15 μM), strongly inhibiting the kinase activity of the enzyme. It displays antiproliferative activity against murine leukemia P388 (IC₅₀ = 0.26 μM), strong anti-HIV-1 activity (IC₅₀ = 0.07 μM in HIV-1 Lai-infected CEM-SS cells) but a low selectivity index (SI = 4.8; CC₅₀ in uninfected CEM-SS cells = 0.34 μM) and antibacterial activity against *Bacillus cereus* (MIC = 19 μM). Considered a useful lead compound for the synthesis of new indolocarbazoles with improved antineoplastic activity.

SOURCES – INSERM; Novartis; Rhône-Poulenc Rorer.

REFERENCES

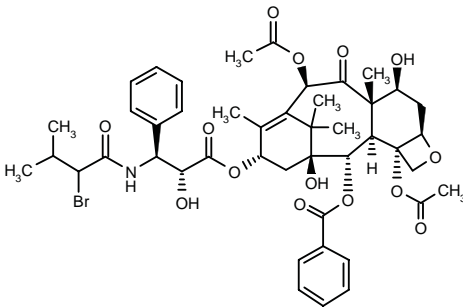
1. Moreau, P. et al. *Synthesis, mode of action, and biological activities of rebeccamycin bromo derivatives*. J Med Chem 1999, 42(10): 1816.

ANTIMITOTIC DRUGS

277010

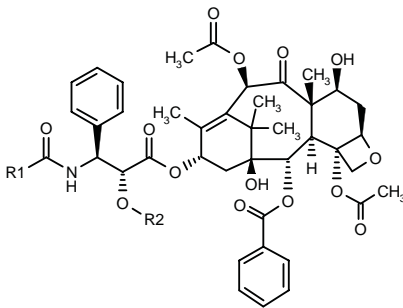
[2*aR*,4*S*,4*aS*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12*aR*,12*bS*]-6,12*b*-Diacetoxy-12-(benzoyloxy)-9-[3-(2-bromo-3-methylbutyramido)-2-hydroxy-3-phenylpropionyloxy]-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-7,11-methano-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-cyclodeca[3,4]-benz[1,2-*b*]oxet-5-one

N-(2-Bromo-3-methylbutanoyl)-*N*-debenzoylpaclitaxel

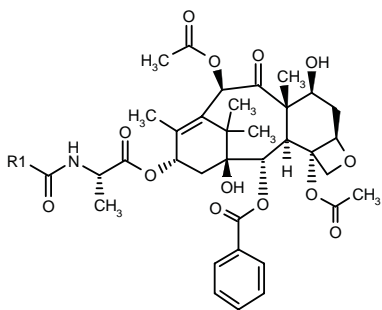


C45 H54 Br N O14; Mol wt: 912.8186

ACTION – Antineoplastic agent, a representative compound from a series of halogenated derivatives of paclitaxel and cephalomannine, wherein the following are also included:



Compound	R1	R2	Formula
277011	2,4-(Br)2-PhO	H	C ₄₇ H ₄₈ Br ₂ NO ₁₅
277012	OCH2CH2Br	H	C ₄₃ H ₅₀ BrNO ₁₅
277013	Ph	COCH(Cl)CH(Cl)Ph	C ₅₆ H ₅₇ Cl ₂ NO ₁₅
277014	Ph	CO2CH2CH(Cl)Me	C ₅₁ H ₅₆ ClNO ₁₆
277015	Ph	2-Cl-PhOCO	C ₅₄ H ₅₄ ClNO ₁₆
277016	Ph	2,4,6-(Br)3-PhOCO	C ₅₄ H ₅₂ Br ₃ NO ₁₆
277017	i-PrCH(Br)	CO2CH2CH2Br	C ₄₈ H ₅₇ Br ₂ NO ₁₆



Compound	R1	Formula
277018	4-Br-Ph	C ₄₁ H ₄₆ BrNO ₁₃
277019	OCH2CH2Cl	C ₃₇ H ₄₆ ClNO ₁₄

SOURCE – Xechem.

REFERENCES

1. Pandey, R.C. and Yankov, L.K. (Xechem International, Inc.) *Halogenated paclitaxel derivs.* WO 9925334.

CANCER IMMUNOTHERAPY

ABX-EGF

276195

Fully human IgG₂ monoclonal antibody generated using XenoMouse™ technology that binds to the epidermal growth factor (EGF) receptor

E7.6.3

ACTION – Antineoplastic agent, a fully human IgG₂ monoclonal antibody to the epidermal growth factor (EGF) receptor (K_D = 50 pM) that completely blocks the binding of both EGF (IC₅₀ = 0.9 nM in human colon carcinoma SW948 cells) and transforming growth factor-α (TGF-α; human epidermoid carcinoma A431 cells) to the EGF receptor on the surface of human carcinoma cell lines; it also abolished EGF-dependent cell activation, including EGF receptor tyrosine phosphorylation and tumor cell proliferation (IC₅₀ = 0.125 nM for inhibition of the growth of A431 cells). *In vivo*, compound (0.2 or 1 mg i.p. twice a week for 3 weeks) completely prevented the development of or eradicated established human epidermoid carcinoma A431 xenografts in nude mice, and significantly inhibited the growth of other carcinomas expressing the EGF receptor such as pancreatic carcinoma BxPC3, HST766T and HPAC, renal carcinoma SK-RC-29 and breast carcinoma MDA-MB-468, whereas it had no effect on SW707 tumors that do not express this receptor.

SOURCE – Abgenix.

REFERENCES

1. Yang, X.-D. et al. *Potent anti-tumor activity of ABX-EGF, a fully human monoclonal antibody to the epidermal growth factor receptor.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1766.

2. Yang, X.D. et al. *Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy.* Cancer Res 1999, 59(6): 1236.

3. *Abgenix files IND for ABX-EGF.* DailyDrugNews.com (Daily Essentials) 1999, July 21.

4. *Abgenix reports encouraging preclinical results with ABX-EGF in cancer research - Fully human antibody eradicates established tumors as monotherapy.* Abgenix, Inc. Press Release 1999, March 15.

5. *Abgenix reports first quarter results.* Abgenix, Inc. Press Release 1999, April 27.

6. *Abgenix reports significant advance in human antibody technology.* DailyDrugNews.com (Daily Essentials) 1997, Feb 6.

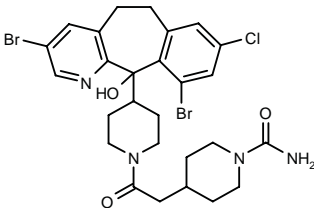
7. *Company Profile: Cell Genesys.* DailyDrugNews.com (Daily Essentials) 1998, Feb 23.

8. Abgenix, Inc. Product Pipeline 1999, June 16.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

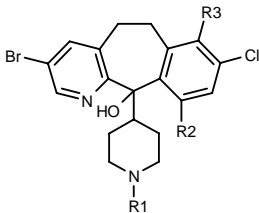
275449

4-[2-[4-(3,10-Dibromo-8-chloro-11-hydroxy-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidin-yl]-2-oxoethyl]piperidine-1-carboxamide



C27 H31 Br2 Cl N4 O3; Mol wt: 654.8279

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. Other specifically claimed benzo[5,6]-cyclohepta[1,2-b]pyridine derivatives include the following:



Compound	R1	R2	R3	Formula
275451	1-(CONH2)-4-Pip-CH2CO	H	Br	C ₂₇ H ₃₁ Br ₂ ClN ₄ O ₃
275452	1-(NH2COCH2)-4-Pip-CH2CO	Br	H	C ₂₈ H ₃₃ Br ₂ ClN ₄ O ₃
275454	1-(NH2COCH2)-4-Pip-CH2CO	H	Br	C ₂₈ H ₃₃ Br ₂ ClN ₄ O ₃
275457	1-(NH2CO)-3-pyrrolidinyl-CH2CO	Br	H	C ₂₆ H ₂₉ Br ₂ ClN ₄ O ₃
275459	1-(NH2CO)-3-pyrrolidinyl-CH2CO	H	Br	C ₂₆ H ₂₉ Br ₂ ClN ₄ O ₃
275460	1-oxido-4-Pyr-CH2CO	Br	H	C ₂₆ H ₂₄ Br ₂ ClN ₃ O ₃
275461	1-oxido-4-Pyr-CH2CO	H	Br	C ₂₆ H ₂₄ Br ₂ ClN ₃ O ₃
275464	SO2Me	Br	H	C ₂₀ H ₂₁ Br ₂ ClN ₂ O ₃ S
275466	SO2Me	H	Br	C ₂₀ H ₂₁ Br ₂ ClN ₂ O ₃ S

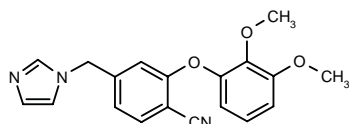
SOURCE – Schering-Plough.

REFERENCES

1. Cooper, A.B. et al. (Schering Corp.) *Benzo(5,6)cyclohepta(1,2b)pyridine derivs. useful for inhibition of farnesyl protein transferase.* WO 9857944.

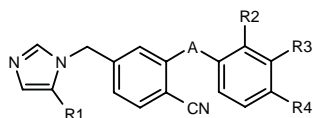
276415

2-(2,3-Dimethoxyphenoxy)-4-(1*H*-imidazol-1-ylmethyl)-benzonitrile



C₁₉ H₁₇ N₃ O₃; Mol wt: 335.3613

ACTION – Antineoplastic agent, an inhibitor of protein prenyltransferases and the farnesylation of the oncogene protein Ras. Other preferred small-molecule phenyl-containing compounds include the following:



Compound	R1	R2	R3	R4	Formula
276416	H	H	-CH=CHCH=CH-		C ₂₁ H ₁₅ N ₃ O
276417	H	Cl	H	Cl	C ₁₇ H ₁₁ Cl ₂ N ₃ S
276418	H	H	CON(Et)Ph	H	C ₂₆ H ₂₂ N ₄ O ₂
276419	4-morpholinyl-CH ₂ CH ₂	Cl	H	Cl	C ₂₃ H ₂₂ Cl ₂ N ₄ OS

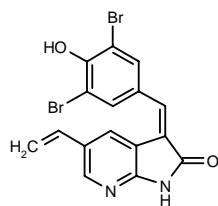
SOURCE – Merck & Co.

REFERENCES

1. Desolms, S.J. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 9917777.

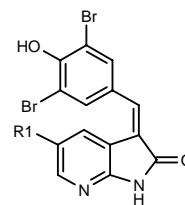
276505

3-(3,5-Dibromo-4-hydroxybenzylidene)-5-vinyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-2-one



C₁₆ H₁₀ Br₂ N₂ O₂; Mol wt: 422.0750

ACTION – Antiproliferative agent, an inhibitor of protein kinases such as CDK2, vascular endothelial growth factor (VEGF) receptor tyrosine kinase and Raf kinase (IC₅₀ < 1 μM). *In vitro*, it was shown to inhibit the proliferation of human colon carcinoma HT-29, human breast carcinoma MDA-468 and human umbilical vein endothelial cells (HUVEC) with IC₅₀ values in the range 1-50 μM. Potentially useful for the treatment of cancer, psoriasis, fibrosis, atherosclerosis, restenosis, autoimmune diseases, allergy, asthma, transplant rejection, inflammation, thrombosis and CNS disorders. Other compounds from this series of azaoxindole derivatives include the following:



Compound	R1	Formula
276507	2-furyl	C ₁₈ H ₁₀ Br ₂ N ₂ O ₃
276510	Et	C ₁₆ H ₁₂ Br ₂ N ₂ O ₂
276511	Br	C ₁₄ H ₇ Br ₃ N ₂ O ₂

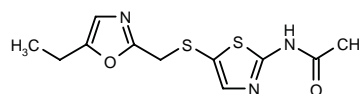
SOURCE – Glaxo Wellcome.

REFERENCES

1. Cheung, M. et al. (Glaxo Group Ltd.) *Azaoxindole derivs*. WO 9921859.

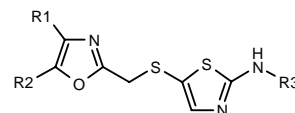
276883

N-[5-(5-Ethylloxazol-2-ylmethylsulfanyl)thiazol-2-yl]-acetamide



C₁₁ H₁₃ N₃ O₂ S₂; Mol wt: 283.3747

ACTION – Agent for the treatment of cancer, inflammation, autoimmune, viral, fungal, neurodegenerative and cardiovascular diseases, an inhibitor of protein kinases, particularly cyclin-dependent kinases (CDK). Other specifically claimed compounds within this series of 2-aminothiazole derivatives include the following:



Compound	R1	R2	R3	Formula
276884	H	Et	COPh	C ₁₆ H ₁₅ N ₃ O ₂ S ₂
276885	H	Et	SO ₂ Ph	C ₁₅ H ₁₅ N ₃ O ₃ S ₃
276886	Me	Me	Ac	C ₁₁ H ₁₃ N ₃ O ₂ S ₂
276887	H	t-Bu	Ac	C ₁₃ H ₁₇ N ₃ O ₂ S ₂
276888	H	t-Bu	t-BuCO	C ₁₆ H ₂₃ N ₃ O ₂ S ₂
276889	Et	H	Ac	C ₁₁ H ₁₃ N ₃ O ₂ S ₂

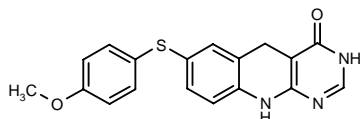
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Kim, K.S. et al. (Bristol-Myers Squibb Co.) *Aminothiazole inhibitors of cyclin dependent kinases*. WO 9924416.

276949

7-(4-Methoxyphenylsulfanyl)-3,4,5,10-tetrahydro-pyrimido[4,5-*b*]quinolin-4-one



C₁₈ H₁₅ N₃ O₂ S; Mol wt: 337.4015

ACTION – Tyrosine kinase inhibitor with potential in the treatment of cancer, angiogenesis, atherosclerosis and other tyrosine kinase-dependent diseases. A representative compound from a series of 5,10-dihydropyrimido[4,5-*b*]quinolin-4(3*H*)-one derivatives.

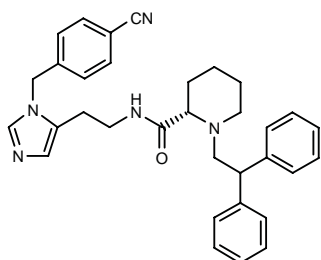
SOURCE – Pfizer.

REFERENCES

1. Dow, R.L. (Pfizer Inc.) 5,10-Dihydropyrimido[4,5-*b*]quinolin-4(1*H*)-one tyrosine kinase inhibitors. US 5908930, WO 9628444.

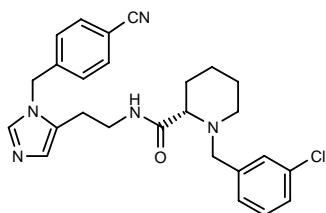
277363

N-[2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]ethyl]-1-(2,2-diphenylethyl)piperidine-2(*S*)-carboxamide



C₃₃ H₃₅ N₅ O; Mol wt: 517.6735

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Also claimed for the prevention of restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed compound from this series of peptidomimetic piperidine derivatives is:



277364: C₂₆ H₂₈ Cl N₅ O

SOURCE – Merck & Co.

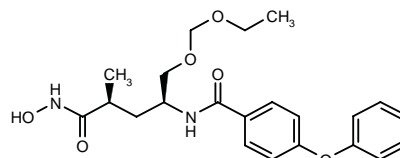
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ANGIOGENESIS INHIBITORS

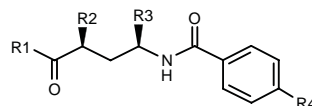
276757

N-[1(*S*)-(Ethoxymethoxymethyl)-4-(hydroxyamino)-3(*S*)-methyl-4-oxobutyl]-4-phenoxybenzamide



C₂₂ H₂₈ N₂ O₆; Mol wt: 416.4712

ACTION – Matrix metalloproteinase (MMP) inhibitor active against human gelatinase A, collagenase and stromelysin (IC₅₀ = 0.50 nM, 2.5 μM and 26 nM, respectively), potentially useful for the treatment and/or prevention of cancer and cancer metastasis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, arteriosclerosis, hepatic cirrhosis, corneal injury, autoimmune diseases, etc. Other representative compounds from this series of aminobutanoic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
276853	NHOH	OH	H	2-benzofuryl	C ₁₉ H ₁₈ N ₂ O ₅
276854	NHOH	H	CONHMe	Me	C ₁₄ H ₁₉ N ₃ O ₄
276855	NHOH	H	CH ₂ OH	2-benzofuryl	C ₂₀ H ₂₀ N ₂ O ₅
276856	OH	allyl	CH ₂ OCH ₂ OEt	OPh	C ₂₄ H ₂₉ NO ₆
276857	NHOH	H	CH ₂ OMe	4-Cl-Ph	C ₁₉ H ₂₀ ClNO ₄

SOURCE – Ono.

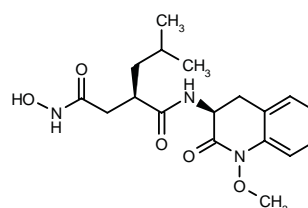
REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) Aminobutanoic acid derivs. WO 9919296.

OPB-3206*

216572

3(*R*)-Isobutyl-4-[1-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3(*S*)-ylamino]-4-oxobutylhydroxamic acid



C₁₈ H₂₅ N₃ O₅; Mol wt: 363.4170

ACTION – Matrix metalloproteinase inhibitor active against gelatinase A (MMP-2; $IC_{50} = 5 \mu M$), gelatinase B (MMP-9; $IC_{50} = 0.5 \mu M$), stromelysin (MMP-3; $IC_{50} = 2 \mu M$) and interstitial collagenase ($IC_{50} = 0.7 \mu M$). In rats, compound (0.4% in the diet for 4 weeks) significantly inhibited the formation of lung metastases from subcutaneously transplanted rat osteosarcoma S-SLM.

SOURCE – Otsuka.

REFERENCES

1. Sakamoto, M. et al. (Otsuka Pharmaceutical Co., Ltd.) *Carbostyryl derivs. as matrix metalloproteinases inhibitors*. EP 641323, JP 95157470, WO 9421612.

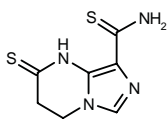
2. Kido, A. et al. *Inhibition of spontaneous rat osteosarcoma lung metastasis by 3S-[4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxy-3,4-dihydrocarbostyryl, a novel matrix metalloproteinase inhibitor*. Jpn J Cancer Res 1999, 90(3): 333.

*Identified compound **216572** (see **215328**) Drug Data Report 1995, 017(02): 0200.

OTHER ONCOLYTIC DRUGS

276571

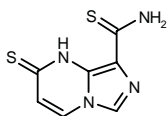
2-Thioxo-1,2,3,4-tetrahydroimidazo[1,5-a]pyrimidine-8-carbothioamide



C7 H8 N4 S2; Mol wt: 212.3002

M.p. 258-62 °C.

ACTION – Antineoplastic agent with strong cytotoxic effect against both murine leukemia L1210 ($IC_{50} = 0.61 \mu M$) and human oral epidermoid carcinoma KB cells ($IC_{50} = 3.2 \mu M$), with potency comparable to 5-fluorouracil ($IC_{50} = 0.61$ and $2.3 \mu M$, respectively). Compound was also active against a variety of human solid tumors including colon carcinoma SW-480, stomach adenocarcinoma MKN-28, lung adenocarcinoma PC-9, breast carcinoma MCF-7 and pancreas adenocarcinoma PANC-1 ($IC_{50} = 3.8$ - $12.3 \mu M$), as well as against human leukemia cells including chronic myelogenous leukemia K562, promyelocytic leukemia HL-660 and Burkitt's lymphoma Daudi cells ($IC_{50} = 1.1$ - $4.1 \mu M$). Another disubstituted imidazo[1,5-a]pyrimidine derivative is:



276574: C7 H6 N4 S2

SOURCE – Minophagen.

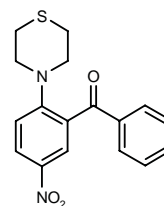
REFERENCES

1. Matsumoto, K. et al. (Minophagen Pharmaceutical Co., Ltd.) *Novel imidazo[1,5-a]pyrimidine derivs. and their preparation*. JP 99092478.

2. Matsumoto, H. et al. *Synthesis of 2,8-disubstituted imidazo[1,5-a]pyrimidines with potent antitumor activity*. J Med Chem 1999, 42(9): 1661.

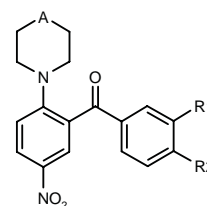
276605

1-[5-Nitro-2-(thiomorpholin-4-yl)phenyl]-1-phenylmethanone



C17 H16 N2 O3 S; Mol wt: 328.3904

ACTION – Antineoplastic agent with cytotoxicity against murine leukemia P388 and human lung cancer PC-6 cells ($GI_{50} = 23$ and 4.89 ng/ml, respectively). *In vivo*, it exhibited antitumor activity in mice bearing murine leukemia P388, with a T/C value of 130% at a dose of 206 mg/kg i.p. x 2. Other exemplified diphenyl compounds include the following:



Compound	R1	R2	A	Formula
276606	H	H	O	C ₁₇ H ₁₆ N ₂ O ₄
276607	H	Cl	O	C ₁₇ H ₁₅ ClN ₂ O ₄
276608	H	Cl	S	C ₁₇ H ₁₅ ClN ₂ O ₃ S
276609	H	Cl	N(Me)	C ₁₈ H ₁₈ ClN ₃ O ₃
276610	H	OMe	N(Me)	C ₁₉ H ₂₁ N ₃ O ₄
276611	H	F	N(Me)	C ₁₈ H ₁₈ FN ₃ O ₃
276612	OMe	OMe	N(Me)	C ₂₀ H ₂₃ N ₃ O ₅

SOURCE – Daiichi Pharmaceutical.

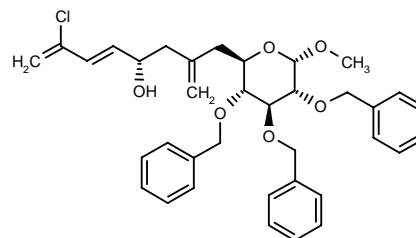
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2. Eto, A. et al. (Daiichi Pharmaceutical Co., Ltd.) *Diphenyl cpds*. JP 99080141.

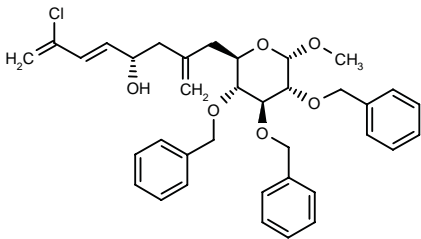
276842

Methyl 2,3,4-tri-O-benzyl-6-desoxy-6-[3(R)-hydroxy-1-methylene-4(E),6-heptadienyl]-α-D-glucopyranoside



C36 H42 O6; Mol wt: 570.7218

ACTION – Cytotoxic agent that mimics the chemical and biological activity of the spongistatins and shows activity against a series of human cancer cell lines such as human pancreatic adenocarcinoma BxPC-3, neuroblastoma SK-N-SH, thyroid carcinoma SW 1736, non-small cell lung NCI-H460, squamous cell carcinoma of the pharynx FaDu and prostate carcinoma DU-145 of (GI₅₀ = 0.44, 0.54, 1.2, 0.46, 0.47 and 0.56 μM, respectively). Another exemplified triene-containing compound is:



276843: C36 H41 Cl O6

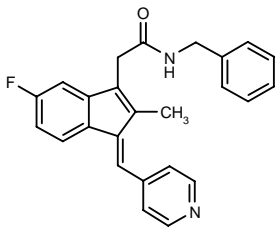
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Smith, A.B. III and Lin, Q. (University of Pennsylvania) *Novel trienyl cpds.* WO 9924030.

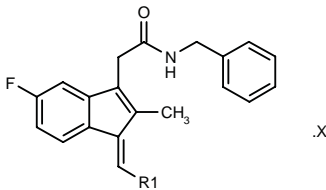
278044

N-Benzyl-2-[5-fluoro-2-methyl-1-[(*Z*)-(pyridin-4-yl)methylene]-1*H*-inden-3-yl]acetamide



C25 H21 F N2 O; Mol wt: 384.4519

ACTION – Antineoplastic agent useful for inducing or promoting apoptosis and arresting uncontrolled neoplastic cell proliferation. Compound potently induces apoptosis in neoplastic cells, but not substantially in normal cells; it also shows no significant inhibition of PGE₂, and is thus expected to be devoid of the side effects of conventional chemotherapeutics and nonsteroidal antiinflammatory drugs. It inhibited cyclooxygenase type 1 (COX-1) to a significantly lesser extent than sulindac sulfide. Other exemplified *N*-benzyl-3-indenylacetamides are:



Compound	R1	X	Formula
278046	3-Pyr		C ₂₆ H ₂₁ FN ₂ O
278047	2-Pyr		C ₂₆ H ₂₁ FN ₂ O
278048	4-quinoliny		C ₂₉ H ₂₃ FN ₂ O
278049	4-Pyr	HCl	C ₂₅ H ₂₀ FN ₂ O.HCl

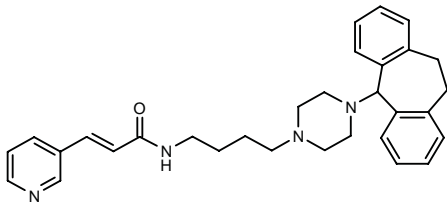
SOURCES – University of Arizona, Tucson, AZ (US); Cell Pathways.

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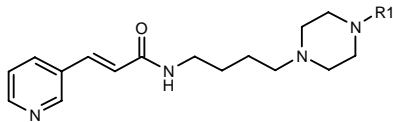
278050

N-[4-[4-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)piperazin-1-yl]butyl]-3-(pyridin-3-yl)-2-propenamide



C31 H36 N4 O; Mol wt: 480.6524

ACTION – Cytostatic and immunosuppressive agent proven to inhibit the proliferation of human colon carcinoma HT-29, human lung carcinoma A549, human hepatocellular carcinoma HepG2 and human monocytic leukemia THP-1 cells with respective IC₅₀ values of 0.2, 0.2, 0.08 and 0.02 μM. Its immunosuppressive activity was demonstrated in murine spleen lymphocytes (IC₅₀ = 0.03 μM). Other representative compounds from this series of piperaziny-substituted pyridylalkane, alkene and alkine carboxamides are:



Compound	R1	Formula
278051	2-Ph-cyclohexyl	C ₂₈ H ₃₈ N ₄ O
278052	9-fluorenyl	C ₂₉ H ₃₂ N ₄ O
278053	1-Naph	C ₂₆ H ₃₀ N ₄ O
278054	1,2,3,4-tetrahydro-1-Naph	C ₂₆ H ₃₄ N ₄ O
278055	PO(Ph)2	C ₂₈ H ₃₃ N ₄ O ₂ P

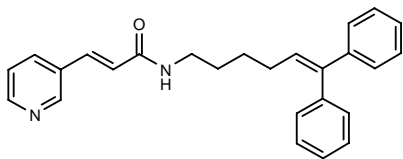
SOURCE – Klinge.

REFERENCES

1. Biedermann, E. et al. (Klinge Pharma GmbH) *New piperaziny-substd. pyridylalkane, alkene and alkine carboxamides.* WO 9931063.

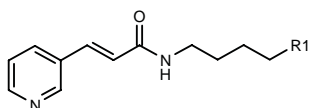
278064

N-(6,6-Diphenylhex-5-enyl)-3-(pyridin-3-yl)-2-propenamide

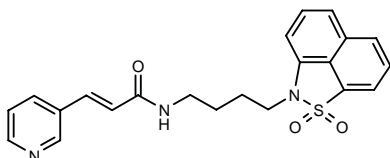


C₂₆ H₂₆ N₂ O; Mol wt: 382.5044

ACTION – Cytostatic and immunosuppressive agent with IC₅₀ values of 2, 0.5 and 0.2 nM, respectively, against human lung carcinoma A549, human hepatocellular carcinoma HepG2 and human monocytic leukemia THP-1 cells. Potent immunosuppressive activity (IC₅₀ = 0.5 nM) was also observed using murine spleen lymphocytes. Other representative compounds from this series of aryl-substituted pyridylalkane, alkene and alkine carboxamides are:



Compound	R1	Formula
278065	CH ₂ C(Ph) ₂ OH	C ₂₆ H ₂₈ N ₂ O ₂
278066	(CH ₂) ₃ CH(Ph) ₂	C ₂₈ H ₃₂ N ₂ O
278067	4,5-(Ph) ₂ -1-imidazolyl	C ₂₇ H ₂₈ N ₄ O



278068: C₂₂ H₂₁ N₃ O₃ S

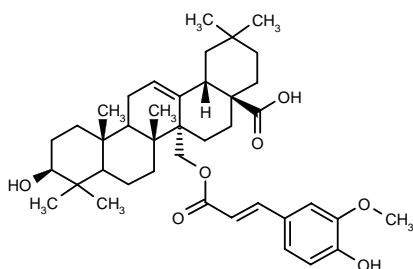
SOURCE – Klinge.

REFERENCES

1. Biedermann, E. et al. (Klinge Pharma GmbH) Aryl-substd. pyridylalkane, alkene, and alkine carboxamides useful as cytostatic and immunosuppressive agents. WO 9931064.

UNCARINIC ACID A^{1,2}**277038**

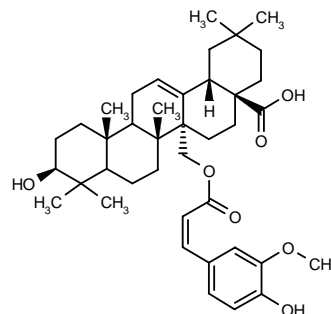
3β-Hydroxy-27-[3-(4-hydroxy-3-methoxyphenyl)-2(*E*)-propenyloxy]olean-12-en-28-oic acid



C₄₀ H₅₆ O₇; Mol wt: 648.8754

White amorphous powder, $[\alpha]_D^{24} +52.6^\circ$ (c 0.8, MeOH).

ACTION – Antineoplastic agent, a phospholipase C γ 1 inhibitor (IC₅₀ = 35.66 μ M) extracted from *Uncaria rhynchophylla* and proven to inhibit the growth of several human adenocarcinoma cell lines such as A-549 (lung), HCT-15 (colon), MCF-7 (breast) and HT-1197 (bladder) cells (IC₅₀ = 0.73, 1.41, 2.03 and 3.53 μ g/ml, respectively). Another related compound is:



Uncarinic acid B [277039]²: C₄₀ H₅₆ O₇

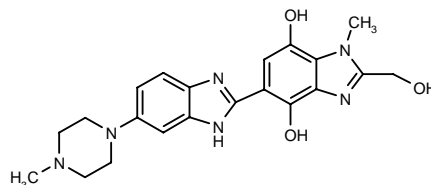
SOURCE – Korea Research Institute of Bioscience and Biotechnology, Taedok Science Town (KR).

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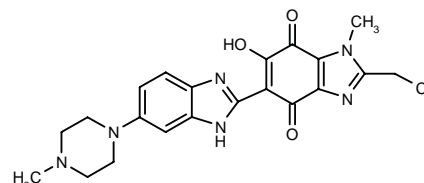
V-93**276477**

2'-(Hydroxymethyl)-1'-methyl-5-(4-methyl-1-piperazinyl)[2,5'-bi-1*H*-benzimidazole]-4',7'-diol



C₂₁ H₂₄ N₆ O₃; Mol wt: 408.4596

ACTION – Antineoplastic agent, a bisbenzimidazole with cytotoxic activity against murine leukemia L1210 cells and human tumor cell lines including T-lymphoblast Molt/4F and nasopharyngeal KB cells (IC₅₀ approx. 1 μ g/ml or less). Compound targets human DNA helicase activity (IC₅₀ = 30 μ M). A related compound is:



V-153 [276478]: C₂₁ H₂₁ Cl N₆ O₃

SOURCE – University of Alberta, Edmonton, AB (CA).

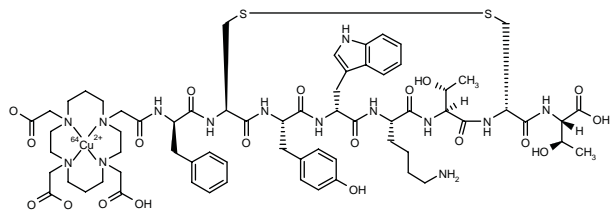
REFERENCES

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[⁶⁴Cu]-TETA-Y3-TATE

275787

[N-[4,8,11-Tris(carboxymethyl)-1,4,8,11-tetraazacyclo-tetradecane-1-ylacetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threonine cyclic (2-7)-disulfidato(2-)]copper[⁶⁴Cu]



C67 H93 Cu N15 O19 S2; Mol wt: 1540.6900

ACTION – ⁶⁴Cu-labeled somatostatin analogue able to bind with high affinity to somatostatin receptors in rat pancreatic tumor CA20948 cell membranes (IC₅₀ = 0.308 nM). Compound showed high uptake (60.75% in 2 h) *in vitro* in rat pancreatic tumor AR42J cells and *in vivo* in somatostatin receptor-rich tissues (pancreas, liver, adrenals and tumor) in rats bearing CA20948 tumors. Potentially useful for positron emission tomography (PET) imaging and targeted radiotherapy.

SOURCE – Mallinckrodt.

REFERENCES

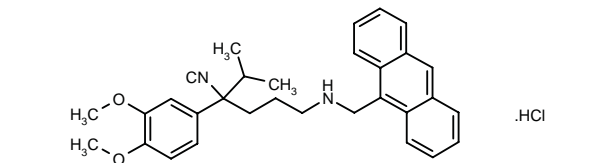
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

MM-36

277041

5-(Anthracen-9ylmethylamino)-2-(3,4-dimethoxyphenyl)-2-isopropylpentanenitrile hydrochloride



C31 H34 N2 O2 . HCl; Mol wt: 503.0825

M.p. 118-20 °C.

ACTION – Potent and selective inhibitor of multidrug resistance (MDR) proven to increase the uptake of pirarubicin in anthracycline-resistant erythroleukemia K562 cells, with an [i]_{0.5} value (concentration that causes a half-maximal increase in nuclear concentrations of pirarubicin) of 0.05 μM and a potency at least 30-fold higher than verapamil. Compound is not active as a vasodilator and showed low cardiovascular activity, with EC₅₀ values of 1.11 and 0.86 μM for negative inotropic and negative chronotropic effects, respectively, in guinea pig atria.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Università degli Studi di Firenze, Firenze (IT).

REFERENCES

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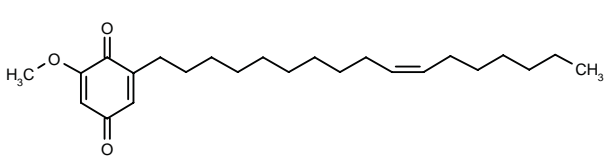
RADIOSENSITIZERS

IRISQUINONE

229421

2-[10(Z)-Heptadecenyl]-6-methoxy-1,4-benzoquinone

lq-7611



C24 H38 O3; Mol wt: 374.5612

ACTION – Antineoplastic and radiosensitizing agent, a quinone derivative extracted from seeds of *Iris pallasii* Fisch. (Iridaceae) found to significantly inhibit the growth of a number of murine tumors. Compound also showed radiosensitizing activity, potentiating the cytotoxic effect of local radiotherapy against mouse uterocervical carcinoma U14, mouse breast cancer Ma737, and hypoxic breast cancer Ma737 and human intestinal mucoadenocarcinoma tumors. A good therapeutic index was observed in mice and a good safety profile was seen in dogs after repeated doses of 4-16 mg/kg/day for 14 days. Multicenter phase III clinical trials demonstrated good radiosensitizing effect against lung and esophageal carcinoma, bone metastatic and superficial metastatic cancers. Compound is a cell cycle-specific agent, arresting cells in the G1 phase and inducing DNA single-strand breaks.

SOURCES – Shandong Xinghua; Shanghai Institute of Pharmaceutical Industry, Shanghai (CN); Tianjin Institute of Materia Medica, Tianjin (CN).

REFERENCES

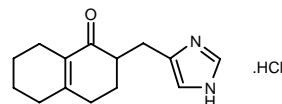
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 11. Li, M.R. et al. *Effect of Iq 7611 on glutathione content in HeLa cells under oxic and hypoxic states*. Chin J Clin Oncol 1987, 14(2): 92.
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- MONOGRAPH – Wang, X.-W. *Irisquinone*. Drugs Fut 1999, 24(6): 0613.

OCULAR MEDICATIONS

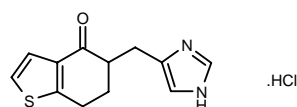
277359

2-(1*H*-Imidazol-4-ylmethyl)-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one hydrochloride



C₁₄ H₁₈ N₂ O . HCl; Mol wt: 266.7701

ACTION – Agent for the treatment of glaucoma, elevated intraocular pressure, chronic pain, diarrhea, nasal congestion, muscle spasticity and neurodegenerative diseases, an α_{2B} -adrenoceptor agonist (intrinsic activity = 0.68 that of oxymetazoline) with selectivity over α_{2C} -adrenoceptors and no activity at α_{2A} -adrenoceptors, and thus expected to cause less side effects than nonselective compounds such as brimonidine and clonidine. *In vivo*, compound produced a $26.9 \pm 6.1\%$ decrease in elevated intraocular pressure (IOP) induced by argon laser photocoagulation in cynomolgus monkeys following ocular administration at a concentration of 0.3%, without any sedative side effects. Negligible blood pressure-lowering activity was observed in monkeys following administration of 500 $\mu\text{g/kg}$ i.v., compared to decreases of 29 ± 7 and $36 \pm 3\%$, respectively, for clonidine and brimonidine at 17 $\mu\text{g/kg}$ i.v. Compound exhibited comparable neuroprotective activity to brimonidine and the neuroprotective agent MK-801 in the calibrated rat optic nerve injury model at 0.5 mg/kg i.p. Another compound from this series of substituted imidazole derivatives is:



277360: C₁₂ H₁₂ N₂ O S . HCl

SOURCE – Allergan.

REFERENCES

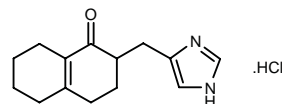
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OCULAR MEDICATIONS

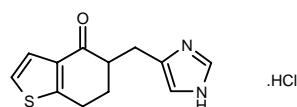
277359

2-(1*H*-Imidazol-4-ylmethyl)-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one hydrochloride



C₁₄ H₁₈ N₂ O . HCl; Mol wt: 266.7701

ACTION – Agent for the treatment of glaucoma, elevated intraocular pressure, chronic pain, diarrhea, nasal congestion, muscle spasticity and neurodegenerative diseases, an α_{2B} -adrenoceptor agonist (intrinsic activity = 0.68 that of oxymetazoline) with selectivity over α_{2C} -adrenoceptors and no activity at α_{2A} -adrenoceptors, and thus expected to cause less side effects than nonselective compounds such as brimonidine and clonidine. *In vivo*, compound produced a $26.9 \pm 6.1\%$ decrease in elevated intraocular pressure (IOP) induced by argon laser photocoagulation in cynomolgus monkeys following ocular administration at a concentration of 0.3%, without any sedative side effects. Negligible blood pressure-lowering activity was observed in monkeys following administration of 500 $\mu\text{g/kg}$ i.v., compared to decreases of 29 ± 7 and $36 \pm 3\%$, respectively, for clonidine and brimonidine at 17 $\mu\text{g/kg}$ i.v. Compound exhibited comparable neuroprotective activity to brimonidine and the neuroprotective agent MK-801 in the calibrated rat optic nerve injury model at 0.5 mg/kg i.p. Another compound from this series of substituted imidazole derivatives is:



277360: C₁₂ H₁₂ N₂ O S . HCl

SOURCE – Allergan.

REFERENCES

1. Chow, K. et al. (Allergan, Inc.) *Substd. imidazole derivs. having agonist-like activity at alpha 2B or 2B/2C adrenergic receptors*. WO 9928300.

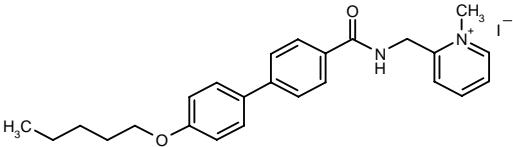
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

276085

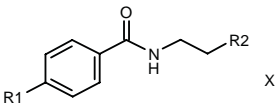
N-(1-Methylpyridinium-2-ylmethyl)-4'-(pentyloxy)biphenyl-4-carboxamide iodide

1-Methyl-2-[4'-(pentyloxy)biphenyl-4-carboxamido-methyl]pyridinium iodide



C25 H29 I N2 O2; Mol wt: 516.4161

ACTION – Agent for the treatment of osteoporosis with osteoblast proliferation-stimulating activity, as demonstrated in an *in vitro* assay using an osteoblast-like cell strain MC3T3-E1 (818 and 1096% increase at 1 and 3 μM, respectively). Other representative compounds within this series of amido derivatives include the following:



Compound	R1	R2	X	Formula
276086	4-(C5H11O)-Ph	CO2Et		C ₂₃ H ₂₉ NO ₄
276087	O(CH2)5Ph	N(Me)2	HCl	C ₂₂ H ₃₀ N ₂ O ₂ ·HCl
276088	(CH2)6Ph	N(Me)3 ⁺	Br ⁻	C ₂₄ H ₃₅ BrN ₂ O

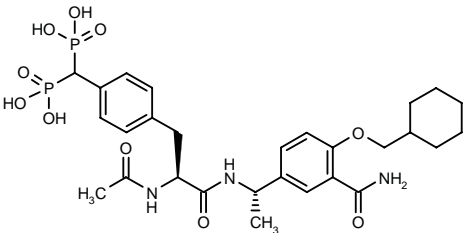
SOURCE – Japan Tobacco.

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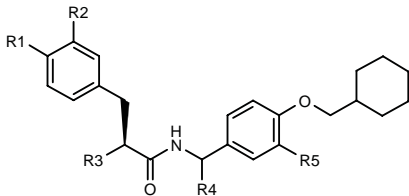
276810

4-[2(S)-Acetamido-3-[1(S)-[3-carbamoyl-4-(cyclohexylmethoxy)phenyl]ethylamino]-3-oxopropyl]-benzylidenediphosphonic acid

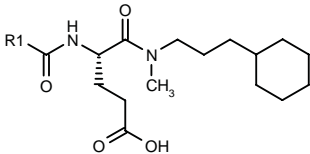


C28 H39 N3 O10 P2; Mol wt: 639.5751

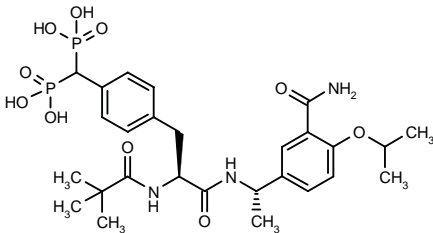
ACTION – Agent for the treatment of osteoporosis, cancer, restenosis, inflammation, allergy and cardiovascular disorders that acts by inhibiting SH₂-mediated signal transduction. Other exemplified compounds include the following:



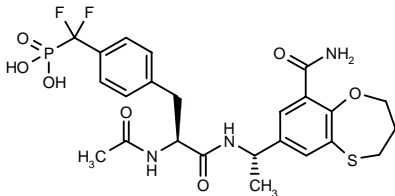
Compound	R1	R2	R3	R4	R5	Formula
276811	CH-(PO3H2)2	H	NHAc	H	H	C ₂₆ H ₃₆ N ₂ O ₉ P ₂
276813	CH(CO2H)-PO3H2	H	NHAc	(S)-Me	CONH2	C ₂₉ H ₃₈ N ₃ O ₉ P
276814	OPO3H2	PO3H2	NHAc	(S)-Me	CONH2	C ₂₇ H ₃₇ N ₃ O ₁₁ P ₂
276815	PO3H2	PO3H2	NHAc	(S)-Me	CONH2	C ₂₇ H ₃₇ N ₃ O ₁₀ P ₂
276816	OCH2-PO3H2	PO3H2	H	Me	CONH2	C ₂₆ H ₃₆ N ₂ O ₁₀ P ₂



Compound	R1	Formula
276817	1-OH-3-oxo-1,3-dihydronaphtho[1,2-c]furan-7-yl	C ₂₆ H ₃₄ N ₂ O ₇
276818	1-OH-3-oxo-1,3-dihydronaphtho[1,2-c]furan-6-yl	C ₂₆ H ₃₄ N ₂ O ₇
276819	5-CHO-6-(OPO3H2)-2-Naph	C ₂₇ H ₃₅ N ₂ O ₉ P



276812: C27 H39 N3 O10 P2



276820: C24 H28 F2 N3 O7 PS

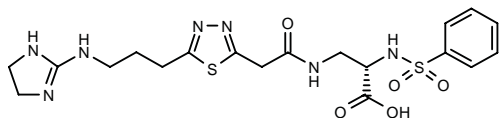
SOURCE – Ariad.

REFERENCES

1. Weigle, M. et al. (Ariad Pharmaceuticals Inc.) *Novel signal transduction inhibitors, compsns. containing them.* WO 9924442.

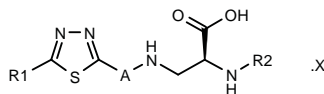
277167

3-[2-[5-[3-(4,5-Dihydro-1H-imidazol-2-ylamino)propyl]-1,3,4-thiadiazol-2-yl]acetamido]-2(*S*)-(phenylsulfonamido)propionic acid



C19 H23 N7 O5 S2; Mol wt: 493.5667

ACTION – Vitronectin ($\alpha_v\beta_3$) receptor antagonist reported to be selective relative to the fibrinogen (gpIIb/IIIa) receptor, with potential in the treatment of angiogenesis, inflammation, bone disorders, cancer, thrombosis, asthma, allergy, septic shock and diabetic retinopathy. Other specifically claimed compounds from this series of 1,3,4-thiadiazoles and 1,3,4-oxadiazoles include the following:



Compound	R1	R2	A	X	Formula
277168	2-imidazolyl-NH(CH ₂) ₃	3-Me-PhSO ₂	-CH ₂ CO-		C ₂₀ H ₂₅ N ₇ O ₅ S ₂
277169	2-Pyr-NH(CH ₂) ₄	CO ₂ CH ₂ Ph	-CO-	CF ₃ CO ₂ H	C ₂₃ H ₂₆ N ₆ O ₅ S .C ₂ HF ₃ O ₂
277170	2-Pyr-NH(CH ₂) ₄	2,4,6-(Me) 3-PhSO ₂	-CO-	CF ₃ CO ₂ H	C ₂₄ H ₃₀ N ₆ O ₅ S ₂ .C ₂ HF ₃ O ₂
277171	2-Pyr-NH(CH ₂) ₄	1-Naph-SO ₂	-CO-	CF ₃ CO ₂ H	C ₂₅ H ₂₆ N ₆ O ₅ S ₂ .C ₂ HF ₃ O ₂
277172	2-imidazolyl-NH(CH ₂) ₄	CO ₂ CH ₂ Ph	-CO-	CF ₃ CO ₂ H	C ₂₁ H ₂₅ N ₇ O ₅ S .C ₂ HF ₃ O ₂
277173	2-imidazolyl-NH(CH ₂) ₄	2,4,6-(Me) 3-PhSO ₂	-CO-	CF ₃ CO ₂ H	C ₂₂ H ₂₈ N ₇ O ₅ S ₂ .C ₂ HF ₃ O ₂
277174	2-imidazolyl-NH(CH ₂) ₄	1-Naph-SO ₂	-CO-	CF ₃ CO ₂ H	C ₂₂ H ₂₈ N ₇ O ₅ S ₂ .C ₂ HF ₃ O ₂

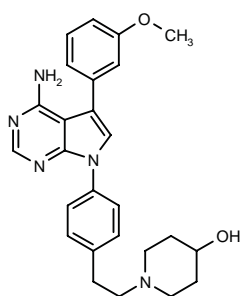
SOURCE – DuPont Pharmaceuticals.

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- Jin, F. and Confalone, P.N. (DuPont Pharmaceuticals Co.) 1,3,4-Thiadiazoles and 1,3,4-oxadiazoles as α phavbeta3 antagonists. WO 9926945.

CGP-77675***262048**

7-[4-[2-(4-Hydroxypiperidin-1-yl)ethyl]phenyl]-5-(3-methoxyphenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine



C26 H29 N5 O2; Mol wt: 443.5481

ACTION – Protein tyrosine kinase pp60 (Src) inhibitor ($IC_{50} = 0.02 \mu M$) with at least 10-fold selectivity over other protein kinases such as epidermal growth factor (EGF) receptor, vascular endothelial growth factor (VEGF) receptor KDR and Flt-1, tyrosine kinase v-Abl and serine/threonine kinase Cdc2, and more than 25-fold selectivity relative to focal adhesion kinase (Fak). Compound concentration-dependently inhibited Src autophosphorylation with an IC_{50} of 40 nM. It was able to inhibit bone resorption induced by parathyroid hormone (PTH) in rat fetal long bone cultures with an IC_{50} of 0.8 $\mu mol/l$. *In vivo* CGP-77675 (1-25 mg/kg/day s.c. for 3 days) significantly reduced hypercalcemia induced by IL-1 β in mice, without affecting serum amyloid protein, and it partially prevented (50 mg/kg p.o. for 6 weeks) bone loss and microstructural changes in vertebral callus bone in ovariectomized rats. Potentially useful for the treatment of diseases associated with bone loss such as postmenopausal osteoporosis, tumor-induced hypercalcemia and Paget's disease.

SOURCE – Novartis.

REFERENCES

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- Missbach, M. et al. A novel inhibitor of the tyrosine kinase Src suppresses phosphorylation of its major cellular substrates and reduces bone resorption in vitro and in rodent models in vivo. Bone 1999, 24(5): 437.

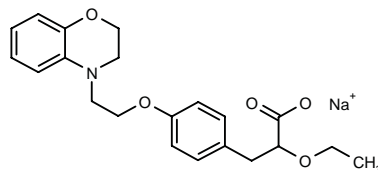
- Missbach, M. et al. Substituted 5,7-diphenylpyrrolo[2,3-*d*]pyrimidines: Potent and specific inhibitors of the tyrosine kinase PP60 c-Src. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 168.

*Identified compound **262048** Drug Data Report 1998, 020(05): 0455.

TREATMENT OF LIPOPROTEIN DISORDERS

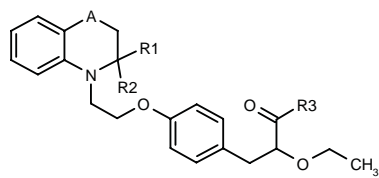
276025

3-[4-[2-(3,4-Dihydro-2H-1,4-benzoxazin-4-yl)ethoxy]-phenyl]-2-ethoxypropionic acid sodium salt

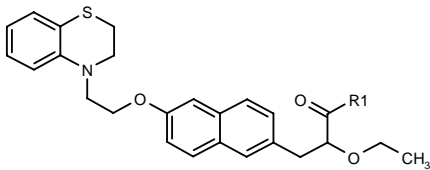


C21 H24 N Na O5; Mol wt: 393.4126

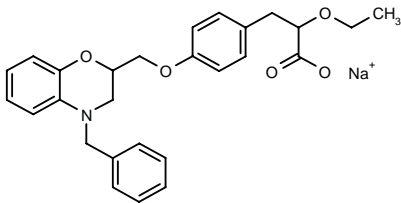
ACTION – Hypocholesterolemic and antiobesity agent with HMG-CoA reductase-inhibitory activity; when tested *in vivo* in hypercholesterolemic rats, at a dose of 1 mg/kg/day p.o. for 3 days it caused a 43% decrease in plasma triglycerides and a 57% decrease in total cholesterol (37% increase in HDL; 58% decrease in LDL and 79% decrease in VLDL). At 10 mg/kg/day p.o. for 15 days, compound produced a 12% reduction in body weight in cholesterol-fed hamsters. Other representative bicyclic compounds include the following:



Compound	R1	R2	R3	A	Formula
276026	H	H	ONa	S	C ₂₁ H ₂₄ NNaO ₄ S
276030	H	H	NH ₂	O	C ₂₁ H ₂₆ N ₂ O ₄
276033	-O-		OH	O	C ₂₁ H ₂₃ NO ₆



Compound	R1	Formula
276035	OH	C ₂₅ H ₂₇ NO ₄ S
276036	ONa	C ₂₆ H ₂₆ NNaO ₄ S



276037: C27 H28 N Na O5

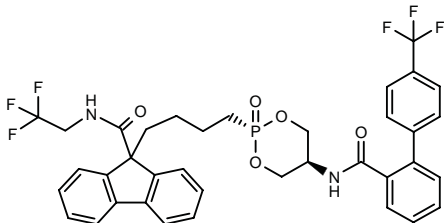
SOURCE – Dr. Reddy’s Research Foundation, Hyderabad (IN).

REFERENCES

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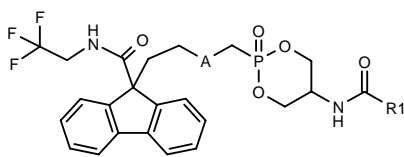
276546

trans-9-[4-[2-Oxo-5-[4’-(trifluoromethyl)biphenyl]-2-ylcarboxamido]-1,3,2λ⁵-dioxaphosphorinan-2-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



C37 H33 F6 N2 O5 P; Mol wt: 730.6387

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor expected to be useful for lowering serum lipid, cholesterol and/or triglyceride levels and for inhibiting and/or treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, hyperglycemia, pancreatitis, obesity or type II diabetes. Other specifically claimed cyclic phosphonate esters include the following:



Compound	R1	A	Isomer	Formula
276547	2-(4-CF3-Ph)-Ph	-CH2-	cis	C ₃₇ H ₃₃ F ₆ N ₂ O ₅ P
276548	Ph	-CH2-	trans	C ₃₀ H ₃₀ F ₃ N ₂ O ₅ P
276550	2-(4-CF3-Ph)-Ph	-(CH2)2-	trans	C ₃₈ H ₃₅ F ₆ N ₂ O ₅ P
276551	2-(4-CF3-Ph)-Ph	-(CH2)2-	cis	C ₃₈ H ₃₅ F ₆ N ₂ O ₅ P
276553	OCH2Ph	-CH2-	trans	C ₃₁ H ₃₂ F ₃ N ₂ O ₆ P
276554	1-(PhCH2)-2-Pip	-CH2-	trans	C ₃₆ H ₄₁ F ₃ N ₃ O ₅ P
276557	2-(2-Pyr)-Ph	-CH2-	trans	C ₃₅ H ₃₃ F ₃ N ₃ O ₅ P
276559	2-(2-benzothiazolyl)-Ph	-CH2-	trans	C ₃₇ H ₃₃ F ₃ N ₃ O ₅ PS
276561	2-(4-morpholinyl)-Ph	-CH2-	trans	C ₃₄ H ₃₇ F ₃ N ₃ O ₆ P
276564	2-(2-benzoxazolyl)-Ph	-CH2-	trans	C ₃₇ H ₃₃ F ₃ N ₃ O ₆ P

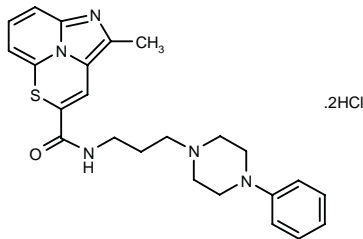
SOURCE – Bristol-Myers Squibb.

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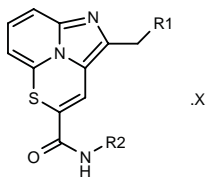
277310

2-Methyl-N-[3-(4-phenylpiperazin-1-yl)propyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride



C25 H28 N4 O S . 2HCl; Mol wt: 505.5110

ACTION – Hypolipidemic and hypoglycemic agent that upregulates LDL receptors, as demonstrated by a 127.0% increase in LDL binding to HepG2 cells at a concentration of 5 μM. Cholesterol-lowering activity was shown in Golden hamsters, non-HDL cholesterol being 68.5% of control and triglycerides 88.4% of control after an oral dose of 20 mg/kg/day x 4 days. Other compounds from this series of fused imidazopyridine derivatives include the following:



Compound	R1	R2	R3	Formula
277311	H	1-[Ph(CH2)3]-4-Pip	3HCl	C ₂₄ H ₂₇ N ₅ OS.3HCl
277312	H	1-[Ph(CH2)3]-4-Pip-CH2	2HCl	C ₂₆ H ₃₀ N ₄ OS.2HCl
277313	H	1-(PhCH2CH2)-4-Pip	2HCl	C ₂₄ H ₂₆ N ₄ OS.2HCl
277314	H	4-Ph-1-Pip-(CH2)4	2HCl	C ₂₆ H ₃₀ N ₄ OS.2HCl
277315	H	1-[2-CN-Ph(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ OS.2HCl
277316	H	1-[3-CN-Ph(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ OS.2HCl
277317	H	1-[4-CN-Ph(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ OS.2HCl
277318	H	1-[2-CN-PhO(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ O ₂ S.2HCl
277319	H	1-[3-CN-PhO(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ O ₂ S.2HCl
277320	H	1-[4-CN-PhO(CH2)3]-4-Pip	2HCl	C ₂₆ H ₂₇ N ₅ O ₂ S.2HCl
277321	OMe	1-[Ph(CH2)3]-4-Pip	2HCl	C ₂₆ H ₃₀ N ₄ O ₂ S.2HCl
277322	OMe	1-[4-CN-Ph(CH2)3]-4-Pip	2HCl	C ₂₇ H ₂₉ N ₅ O ₂ S.2HCl

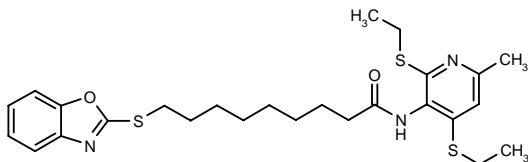
SOURCE – Takeda.

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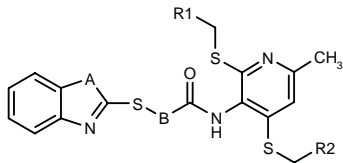
278116

9-(Benzoxazol-2-ylsulfanyl)-N-[2,4-di(ethylsulfanyl)-6-methylpyridin-3-yl]nonanamide



C26 H35 N3 O2 S3; Mol wt: 517.7795

ACTION – ACAT inhibitor proven to exhibit IC₅₀ values of 0.0056 and 0.016 μM, respectively, for enzyme prepared from hypercholesterolemic rabbit thoracic aorta and normal rabbit small intestine; respective IC₅₀ values in J774 and HepG2 cells for this compound were found to be 0.062 and 0.063 μM. Other representative compounds include the following:



Compound	R1=R2	A	B	Formula
278117	H	S	-(CH2)5-	C ₂₁ H ₂₅ N ₃ OS ₄
278118	Me	O	-CH2-	C ₁₉ H ₂₁ N ₃ O ₂ S ₃
278119	Me	O	-(CH2)5-	C ₂₃ H ₂₉ N ₃ O ₂ S ₃
278120	Me	NH	-CH2-	C ₁₉ H ₂₂ N ₄ OS ₃

SOURCE – Kowa.

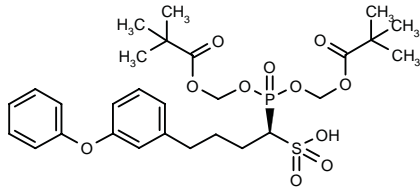
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BMS-188494*1-7,9,13-18

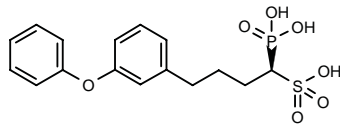
211334

1-(S)-[Bis(pivaloyloxymethoxy)phosphoryl]-4-(3-phenoxyphenyl)butanesulfonic acid



C28 H39 O11 P S; Mol wt: 614.6540

ACTION – Hypolipidemic and hypocholesterolemic agent, an orally active bisester prodrug of the chiral squalene synthase inhibitor **BMS-187745** (K_i = 7.6 nM). Compound given orally to rats inhibited cholesterol biosynthesis with an ID₅₀ of 1.6 mg/kg. In marmosets, compound (25 mg/kg/day for 14 days) inhibited total cholesterol by 56% and both VLDL and LDL cholesterol by 70%, being 10-fold more potent than lovastatin. In a double-blind, placebo-controlled, multiple-dose study in 46 healthy male volunteers, compound was administered at oral doses of 10, 25, 50, 100 or 200 mg/day for 2 weeks and a bioavailability of 16-19.7% was calculated.



BMS-187745 [211332]**1,3,5-12,14-16; C16 H19 O7 P S

SOURCE – Bristol-Myers Squibb.

REFERENCES

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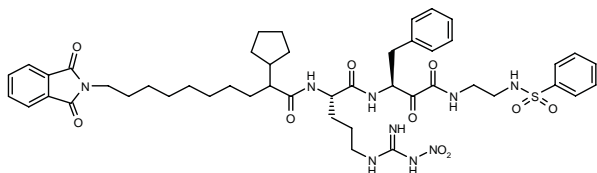
*Identified compound **211334** (see **210142**) Drug Data Report 1994, 016(09): 0842.

Identified compound **211332 (see **210142**) Drug Data Report 1994, 016(09): 0842.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

275708

2-Cyclopentyl-10-phthalimidodecanoyl-L-(*N*^ω-nitro)arginyl-L-phenylalanyl-1-carboxylic acid 2-(phenylsulfonamido)ethylamide



C47 H61 N9 O10 S; Mol wt: 944.1179

ACTION – Agent for retarding abnormal loss of muscle mass in several disease states such as aging, cancer and muscular dystrophy. Compound inhibits α -ketoamide multicatalytic protease ($IC_{50} = 2$ nM), an enzyme complex also referred to as the proteasome that plays a role in at least two cellular pathways for the breakdown of protein to peptides and amino acids. The compound inhibited the growth of murine melanoma B16-F0 tumors in female mice at a dose of 10 mg/kg/day i.p. for 9 days.

SOURCE – Cephalon.

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PEG-OB PROTEIN

276986

Pegylated recombinant human OB protein

Pegylated OB protein

Pegylated leptin

PEG-Leptin

PEG-OB

ACTION – Pegylated recombinant human OB protein with a longer plasma half-life compared to the nonpegylated protein. In a randomized, double-blind, placebo-controlled study in obese males, PEG-OB (20 mg s.c. for 12 weeks), significantly decreased both plasma triglycerides and cholesterol (17.2 and 4.2%, respectively), and it was also able to reduce hunger and increase satiety before breakfast in obese men under energy-restricted conditions.

SOURCE – Roche.

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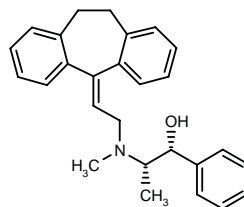
TRECADRINE

Rec INN

109850

$\alpha(R)$ -[1(*S*)-[*N*-[2-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)ethyl]-*N*-methylamino]ethyl]-benzenemethanol

WAS-4304



C27 H29 N O; Mol wt: 383.5321

ACTION – β_3 -Adrenoceptor agonist ($pD_2 = 5.86$ for relaxation of rat esophageal muscularis mucosae) with little or no activity at β_1 - and β_2 -adrenoceptors. In an everted intestinal sac preparation, compound was shown to inhibit galactose uptake and galactose transport. In diabetic rats, a dose of 1 mg/kg p.o. for 3 days induced a significant decrease in plasma glucose and triglyceride levels (65 and 90%, respectively), a decrease of intestinal absorption of galactose and an increase in oxygen consumption in adipose tissue, but not in liver. In a study in cafeteria diet-induced obese rats, compound (0.5 mg/kg/day for 2 weeks) reduced both body weight (9%) and body fat content (49%), increased brown adipose tissue oxygen consumption (23%) and rectal temperature (2.5%), and increased lipolysis in adipose tissue (> 300%). Compound was shown to inhibit the intestinal absorption of galactose not only in pathophysiological conditions, but also in normal rats. Potentially useful in the treatment of obesity and diabetes.

SOURCE – Sociedad Española de Especialidades Farmaco-Terapéuticas.

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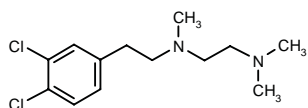
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TREATMENT OF POISONING AND DRUG DEPENDENCY

BD-1047^{1,2,4-11}

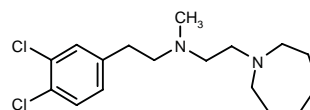
205383

N^1 -[2-(3,4-Dichlorophenyl)ethyl]- N^1,N^2,N^2 -trimethyl-1,2-ethanediamine



C13 H20 Cl2 N2; Mol wt: 275.2210

ACTION – High-affinity σ -receptor ligand with selectivity for σ_1 - over σ_2 -receptors ($K_i = 0.9$ and 47 nM, respectively) and negligible affinity for dopamine, κ -opioid and phencyclidine (PCP) receptors ($IC_{50} > 10 \mu M$) and micromolar affinity for 5-HT₂ receptors ($IC_{50} = 2.26 \mu M$). Compound showed functional antagonist activity in σ -receptor-mediated systems. Behavioral studies in mice demonstrated that compound was able to provide significant protection against cocaine-induced convulsions (protective doses: 1-40 mg/kg i.p.) and lethality (protective doses: 0.5-1 mg/kg i.p.), as well as against cocaine-induced locomotor activity (protective doses: 5-30 mg/kg i.p.). A potential lead compound in the development of new pharmacotherapies for cocaine overdose and addiction. Another related compound is:



LR-172 [277025]:^{1-3,6,9,10} C17 H26 Cl2 N2

SOURCES – National Institutes of Health, Bethesda, MD (US); Searle.

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1. De Costa, B.R. et al. (G.D. Searle & Co.) *N-(Arylethyl)-N-alkyl-2-(1-pyrrolidinyl)ethanamine derivs. for CNS disorders*. EP 518216, WO 9222279.
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8. Tran, T.T. et al. *Microinjection of sigma ligands into cranial nerve nuclei produces vacuous chewing in rats*. Psychopharmacology 1998, 137(2): 191.
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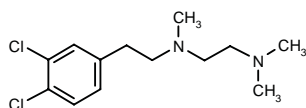
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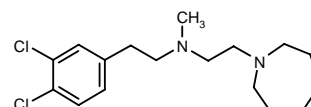
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DIAGNOSTIC AGENTS

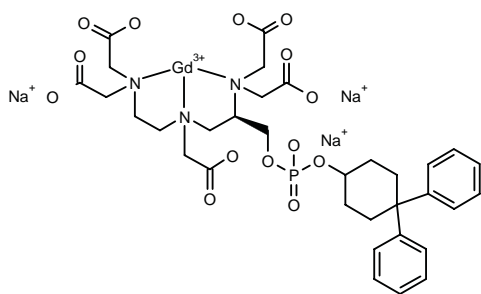
MS-325

235379

Trisodium [2(R)-[(4,4-diphenylcyclohexy)(hydroxy)phosphoryloxymethyl]diethylenetriaminopentaacetato(6-)-gadolate(3-)]

Trisodium (SA-8-11252634)-[[4(R)-[bis[(carboxy-κO)-methyl]amino-κN]-6,9-bis[(carboxy-κO)methyl]-1-(4,4-diphenylcyclohexyloxy)-1-hydroxy-2-oxa-6,9-diaza-1-phosphaundecan-11-oic acid-κN⁶,κN⁹,κO¹¹]-1-oxidato(6-)]gadolate(3-)]

AngioMARK™



C33 H38 Gd N3 Na3 O14 P; Mol wt: 957.8642

ACTION – Small-molecule intravascular magnetic resonance imaging (MRI) contrast agent, a gadolinium chelate that binds to albumin and improves the capability of MRI in multiple cardiovascular indications, including peripheral, carotid and coronary artery disease and atherosclerotic occlusive disease. Phase III clinical trials assessing its use for the detection of aortoiliac disease in patients with known or suspected peripheral vascular disease or abdominal aortic aneurysm are in progress, and it is also being evaluated for the detection of coronary artery disease and breast cancer.

SOURCES – Daiichi Radioisotope; Epix Medical; Mallinckrodt.

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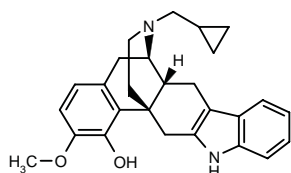
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35. *Progression of Epix Medical's diagnostic agent to phase II triggers milestone payment.* DailyDrugNews.com (Daily Essentials) 1997, July 11.

PHARMACOLOGICAL TOOLS

276771

N-(Cyclopropylmethyl)-3-methoxy-6,7-didehydro-1'*H*-indolo[2',3':6,7]morphinan-4-ol



C27 H30 N2 O2; Mol wt: 414.5460

ACTION – High-affinity δ -opioid receptor ligand ($K_i = 7$ nM against [3 H]-DADLE binding in rat brain membranes) with high selectivity (> 1000 -fold) versus μ - and κ -opioid receptors, at least 100-fold higher than that of naltrindole. In functional studies, compound exhibited weak agonist activity in electrically stimulated guinea pig ileal longitudinal muscle myenteric plexus and mouse vas deferens ($IC_{50} = 532$ and 187.5 nM, respectively) and potent antagonist activity in the GTP- γ S binding assay in guinea pig caudate ($K_i = 22.1$ nM). It is considered to be useful as a new lead for the discovery of highly selective δ -opioid receptor ligands.

SOURCES – University of Arizona, Tucson, AZ (US); National Institute on Drug Abuse, Bethesda, MD (US); National Institutes of Health, Bethesda, MD (US).

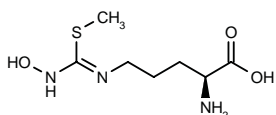
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277048

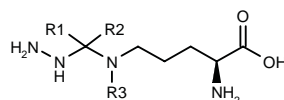
N^{ω} -[(Hydroxyamino)(methylsulfanyl)methylidene]-L-lysine

N^3 -[4(*S*)-Amino-4-carboxybutyl]- N^1 -hydroxy-*S*-methylisothiourea



C7 H15 N3 O3 S; Mol wt: 221.2795

ACTION – Nitric oxide synthase (NOS) inhibitor proven to antagonize in a surmountable manner inducible NOS (iNOS), with a K_i of 7μ M. In the NOS-mediated citrulline formation assay, compound was able to inhibit both the constitutive isoforms of the enzyme (endothelial NOS [eNOS] and neuronal NOS [nNOS]) and iNOS ($IC_{50} = 19.7$, 6.7 and 13μ M, respectively), exhibiting slight selectivity for the neuronal isoform. Compound decreased the NADPH oxidase activity of the enzyme ($IC_{50} = 6.6 \mu$ M) and shifted the heme iron spin state towards a high-spin configuration. Other sulfur-containing L-arginine derivatives with a similar profile are:



Compound	R1	R2	R3	Formula
277047		-S-	H	$C_6H_{14}N_4O_2S$
277050	SMe	bond		$C_7H_{16}N_4O_2S$

SOURCES – Lerner Research Institute, Cleveland, OH (US); Wake Forest University, Winston-Salem, NC (US).

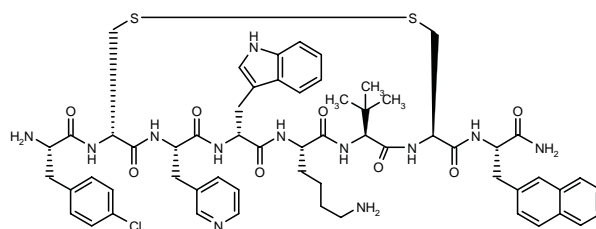
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PRL-2915

277089

4-Chloro-L-phenylalanyl-D-cysteinyl-3-(3-pyridyl)-L-alanyl-D-tryptophyl-L-lysyl-3-(methyl)-L-valyl-L-cysteinyl-3-(2-naphthyl)-L-alaninamide cyclic (2 \rightarrow 7) disulfide



C59 H71 Cl N12 O8 S2; Mol wt: 1175.8710

ACTION – Somatostatin receptor antagonist with nanomolar affinity for cloned human sst2 receptors ($K_i = 12$ nM) and good selectivity over sst3, sst4 and sst1 receptors ($K_i = 100$, 895 and >1000 nM, respectively). In functional studies in rat anterior pituitary cells, compound showed full antagonist activity ($IC_{50} = 1.8$ nM) against somatostatin-induced inhibition of growth hormone secretion. Potentially useful as a pharmacological tool for elucidating the physiological role of somatostatin.

SOURCES – Biomeasure; Tulane University, New Orleans, LA (US).

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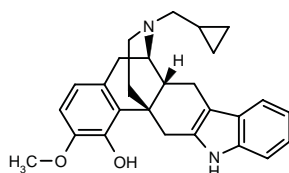
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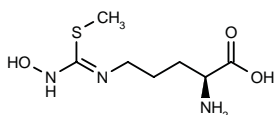
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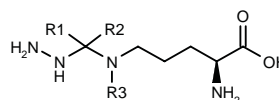
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Compound	R1	R2	R3	Formula
277047		-S-	H	$C_6H_{14}N_4O_2S$
277050	SMe	bond		$C_7H_{16}N_4O_2S$

SOURCES – Lerner Research Institute, Cleveland, OH (US); Wake Forest University, Winston-Salem, NC (US).

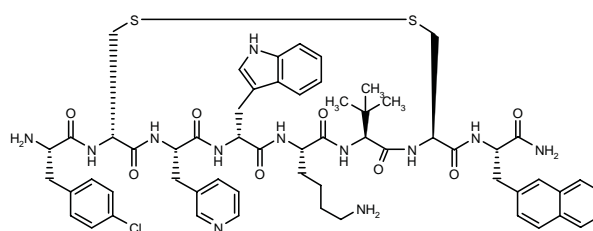
REFERENCES

1. Ichimori, K. et al. *Synthesis and evaluation of new sulfur-containing L-arginine-derived inhibitors of nitric oxide synthase.* J Med Chem 1999, 42(10): 1842.

PRL-2915

277089

4-Chloro-L-phenylalanyl-D-cysteinyl-3-(3-pyridyl)-L-alanyl-D-tryptophyl-L-lysyl-3-(methyl)-L-valyl-L-cysteinyl-3-(2-naphthyl)-L-alaninamide cyclic (2 \rightarrow 7) disulfide



C59 H71 Cl N12 O8 S2; Mol wt: 1175.8710

ACTION – Somatostatin receptor antagonist with nanomolar affinity for cloned human sst2 receptors ($K_i = 12$ nM) and good selectivity over sst3, sst4 and sst1 receptors ($K_i = 100$, 895 and >1000 nM, respectively). In functional studies in rat anterior pituitary cells, compound showed full antagonist activity ($IC_{50} = 1.8$ nM) against somatostatin-induced inhibition of growth hormone secretion. Potentially useful as a pharmacological tool for elucidating the physiological role of somatostatin.

SOURCES – Biomeasure; Tulane University, New Orleans, LA (US).

REFERENCES

1. Morgan, B. et al. (Biomeasure Inc.; Tulane Educational Fund) *Somatostatin antagonists.* WO 9824807.

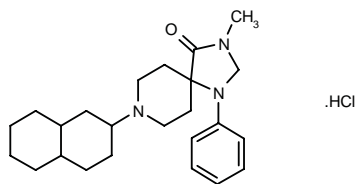
2. Hocart, S.J. et al. *Highly potent cyclic disulfide antagonists of somatostatin.* J Med Chem 1999, 42(11): 1863.

**ANALGESIC AND ANESTHETIC
DRUGS**

ANALGESIC DRUGS

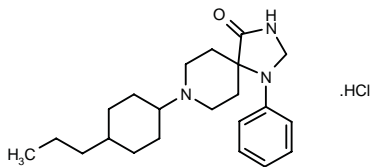
277427

3-Methyl-8-(perhydronaphthalen-2-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one hydrochloride



C₂₄ H₃₅ N₃ O . HCl; Mol wt: 418.0214

ACTION – Orphanin FQ (OFQ, or nociceptin) receptor (ORL1 receptor) agonist and/or antagonist ($pK_i = 9.5$ in a binding assay using rat receptor) expected to be useful in the treatment of memory and attention deficits such as in Alzheimer's disease, anxiety, stress disorders, depression, trauma, epilepsy and convulsions, acute and chronic pain, symptoms of withdrawal from drugs of abuse, for the control of water balance, Na⁺ excretion and arterial blood pressure, and for the treatment of metabolic disorders such as obesity. Another exemplified 1,3,8-triazaspiro[4.5]decan-4-one derivative is:



277428: C₂₂ H₃₃ N₃ O . HCl

OFQ is a 17-amino-acid peptide which is a natural ligand for a G-protein-coupled receptor found at high levels in brain tissue, and it has been suggested to act as a brain neurotransmitter to modulate nociceptive and locomotor behavior.

SOURCE – Roche.

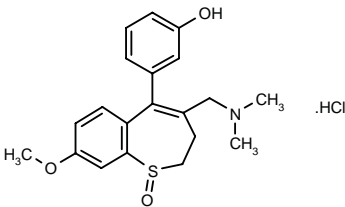
REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) *1,3,8-Triaza-spiro 4,5 decan-4-on derivs.* CA 2255171, EP 921125.

277686

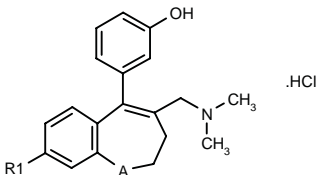
4-(Dimethylaminomethyl)-5-(3-hydroxyphenyl)-8-methoxy-2,3-dihydro-1-benzothiepine S-oxide hydrochloride

3-[4-(Dimethylaminomethyl)-8-methoxy-1-oxo-2,3-dihydro-1-benzothiepin-5-yl]phenol hydrochloride



C₂₀ H₂₃ N O₃ S . HCl; Mol wt: 393.9326

ACTION – Analgesic agent with high affinity and selectivity for δ -opioid receptors ($K_i = 1.44$ nM). A representative compound from a series of substituted heterobicyclic derivatives, wherein the following are also included:



Compound	R1	A	Formula
277687	H	-S-	C ₁₉ H ₂₁ NOS.HCl
277688	H	-O-	C ₁₉ H ₂₁ NO ₂ .HCl
277689	OMe	-O-	C ₂₀ H ₂₃ NO ₃ .HCl
277690	H	-SO-	C ₁₉ H ₂₁ NO ₂ S.HCl
277691	OH	-S-	C ₁₉ H ₂₁ NO ₂ S.HCl
277692	OMe	-S-	C ₂₀ H ₂₃ NO ₂ S.HCl

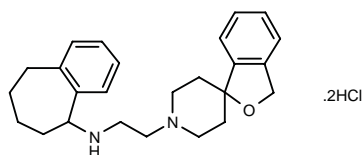
SOURCE – Grünenthal.

REFERENCES

1. Zimmer, O. et al. (Grünenthal GmbH) *Substd. heterocyclic benzocycloalkenes and their use as analgesically active cpds.* CA 2256007, DE 19755480, EP 922703.

277804

N-[2-[Spiro(1,3-dihydroisobenzofuran-1,4'-piperidin)-1'-yl]ethyl]-*N*-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)amine dihydrochloride



C₂₅ H₃₂ N₂ O . 2HCl; Mol wt: 449.4626

ACTION – Orphanin FQ (OFQ, or nociceptin) receptor (ORL1 receptor) antagonist ($pK_i = 7.0$ in a binding assay) expected to be useful in the treatment of memory and attention deficits, anxiety, stress disorders, depression, Alzheimer's disease and other dementias, epilepsy, convulsions, acute and chronic pain and symptoms of addictive drug withdrawal, control of water balance, Na⁺ excretion, arterial blood pressure disorders and obesity.

Orphanin FQ is a 17-amino-acid peptide found in high levels in brain tissue which has been suggested to act as a brain neurotransmitter to modulate nociceptive and locomotor behavior.

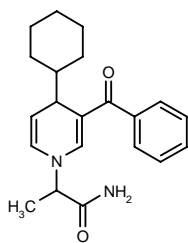
SOURCE – Roche.

REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) *Piperidine derivs.* WO 9929696.

278250¹

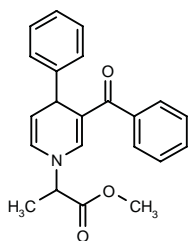
2-(3-Benzoyl-4-cyclohexyl-1,4-dihydropyridin-1-yl)-propionamide



C₂₁ H₂₆ N₂ O₂; Mol wt: 338.4484

M.p. 90-2 °C.

ACTION – Analgesic agent proven to inhibit NaCl-induced writhing in rats (95% at 50 mg/kg i.p.) with efficacy superior to that of acetylsalicylic acid (58% at 50 mg/kg i.p.). Another related compound is:



278251^{1,2}: C₂₂ H₂₁ N O₃

SOURCES – University of Alberta, Edmonton, AB (CA); University of Calgary, Calgary, AB (CA).

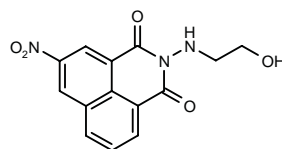
REFERENCES

1. Agudoawu, S.A. et al. *Synthesis and analgesic activity of 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid methyl esters, acetic acids, and acetamides.* Arch Pharm 1999, 332(6): 213.

2. Agudoawu, S.A. et al. *Synthesis of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid methyl ester, acetic acid, and acetamide analogs as potential antiarthritic agents.* Can J Chem 1997, 75(8): 1106.

ALE-0540***264866**

2-(2-Hydroxyethylamino)-5-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione



C₁₄ H₁₁ N₃ O₅; Mol wt: 301.2569

ACTION – Small-molecule nerve growth factor (NGF) receptor antagonist able to inhibit NGF binding to tyrosine kinase A (TrkA) or to both p75 and TrkA receptors ($IC_{50} = 5.88$ and $3.72 \mu M$, respectively, in PC12 cells) without interacting with other receptors including known analgesic targets such as adenosine A₃ and A₁, histamine H₁, ET_A, cannabinoid CB₂, opioid μ -, δ - and κ - receptors and 5-HT_{2A} receptors, nor with NGF receptors. Compound concentration-dependently inhibited NGF-induced neurite outgrowth ($0.1-50 \mu M$) in embryonic chick dorsal root ganglia (DRG) neurons and prevented NGF-induced phosphorylation of TrkA receptors ($EC_{50} = 28 \mu M$). ALE-0540 was effective in a neuropathic pain model (L5/L6 nerve ligation) in rats, blocking tactile allodynia after i.p. or spinal intrathecal (i.t.) administration ($A_{50} = 38$ mg/kg i.p., $34.6 \mu g/rat$ i.t.), but it was inactive (up to $100 \mu g$) when given intracerebroventricularly (i.c.v.); compared to i.p. morphine ($A_{50} = 7.1$ mg/kg i.p.), compound showed lower potency but equal efficacy, but morphine was inactive following i.t. administration at up to $100 \mu g$. Compound also blocked tactile allodynia in the thermal sensitization model in rats at doses of 30 and 60 mg i.t.

SOURCE – Allelix Biopharmaceuticals.

REFERENCES

1. Tehim, A. and Chen, X. (Allelix Biopharmaceuticals Inc.) *Neurotrophin antagonist compns.* EP 930883, WO 9817278.

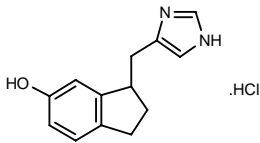
2. Owolabi, J.B. et al. *Characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat.* J Pharmacol Exp Ther 1999, 289(3): 1271.

*Identified compound **264866** Drug Data Report 1998, 020(07): 0572.

MPV-2426*

251317

3-(1*H*-Imidazol-4-ylmethyl)indan-5-ol hydrochloride



C13 H14 N2 O . HCl; Mol wt: 250.7300

ACTION – Analgesic agent, a potent α_2 -adrenoceptor (AR) agonist with high affinity (K_i = 1.0, 1.7 and 2.1 nM, respectively, for α_{2A} -, α_{2B} - and α_{3C} -AR) and full agonist efficacy at all three subtypes. Compound inhibited electrically evoked contractions in rat vas deferens with a pD_2 value of 8.2. In pithed rats, it inhibited the electrically induced tachycardic response (50% inhibition at 0.10 μ g/kg) and increased mean arterial pressure (50 mmHg at 0.23 μ g/kg). Compound showed analgesic activity in the rat tail-flick test (ED_{50} = 0.7 μ g/rat i.t.) and weak sedative potency (ED_{50} = 30 μ g/rat i.t.), giving a sedation/analgesia ratio (43) higher than the reference compound clonidine (0.8). Potentially useful as a spinal analgesic for clinical use.

SOURCE – Orion Corporation.

REFERENCES

1. Karjalainen, A. et al. (Orion Corporation) *Imidazole derivs. having affinity for α_2 receptors activity*. EP 888309, WO 9712874.

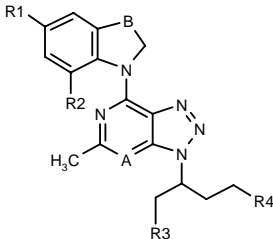
2. Lehtimäki, J. et al. *MPV-2426, a novel α_2 -adrenergic agonist for spinal analgesia*. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PW166.

3. Pertovaara, A. and Wei, H. *MPV-2426, a novel α_2 -adrenoceptor agonist, in neuropathic rats*. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 520.

4. Xu, M. et al. *The effects of MPV-2426, a novel α_2 -adrenergic agonist in different pain models*. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 520.

*Identified compound **251317** (see **251161**) Drug Data Report 1997, 019(07): 0664.

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist claimed for the treatment of a broad range of disorders including affective disorder, anxiety, depression, headache, posttraumatic stress disorder, supranuclear palsy, epilepsy, stroke, irritable bowel syndrome, immune suppression, Alzheimer’s disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, cardiovascular disorders, obesity or fertility disorders. Other specifically claimed compounds from this series of heterocyclyl-substituted ring-fused pyridines and pyrimidines include the following:



Compound	R1	R2	R3	R4	A	B	Formula
275145	Et	Cl	Me	OMe	N	-CH2-	C ₂₁ H ₂₇ ClN ₆ O
275146	SO2Me	Cl	Me	OMe	N	-CH2-	C ₂₀ H ₂₅ ClN ₆ O ₃ S
275147	Br	Br	OMe	OMe	CH	-CH2-	C ₂₀ H ₂₃ Br ₂ N ₅ O ₂
275148	OMe	Cl	OMe	H	CH	-CH2-	C ₂₀ H ₂₄ ClN ₅ O ₂
275150	SO2Me	Cl	Me	H	CH	-CH2-	C ₂₀ H ₂₄ ClN ₅ O ₂ S
275151	Cl	Cl	CH2OMe	OMe	CH	-CH2-	C ₂₁ H ₂₅ Cl ₂ N ₅ O ₂
275152	CN	Cl	Me	H	CH	-CH2-	C ₂₀ H ₂₁ ClN ₆
275153	Me	Cl	Me	H	CH	-(CH2)2-	C ₂₁ H ₂₆ ClN ₅
275154	Ac	Cl	Me	H	CH	-(CH2)2-	C ₂₂ H ₂₆ ClN ₅ O

SOURCE – DuPont Pharmaceuticals.

REFERENCES

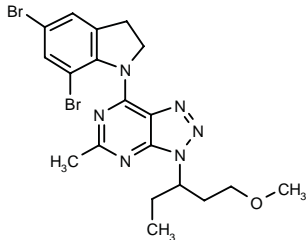
1. Arvanitis, A.G. et al. (DuPont Pharmaceuticals Co.) *Heterocyclyl-substd. ring-fused pyridines and pyrimidines as corticotropin releasing hormone (CRH) antagonists, useful for treating CNS and stress-related disorders*. WO 9911643.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

275144

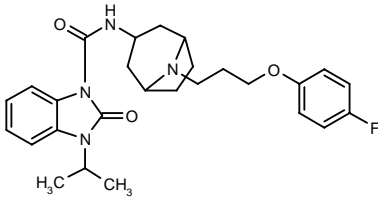
7-(5,7-Dibromo-2,3-dihydro-1*H*-indol-1-yl)-3-(1-ethyl-3-methoxypropyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine



C19 H22 Br2 N6 O; Mol wt: 510.2318

275776

N-[8-[3-(4-Fluorophenoxy)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide

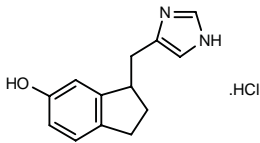


C27 H33 F N4 O3; Mol wt: 480.5807

MPV-2426*

251317

3-(1*H*-Imidazol-4-ylmethyl)indan-5-ol hydrochloride



C13 H14 N2 O . HCl; Mol wt: 250.7300

ACTION – Analgesic agent, a potent α_2 -adrenoceptor (AR) agonist with high affinity (K_i = 1.0, 1.7 and 2.1 nM, respectively, for α_{2A} -, α_{2B} - and α_{3C} -AR) and full agonist efficacy at all three subtypes. Compound inhibited electrically evoked contractions in rat vas deferens with a pD_2 value of 8.2. In pithed rats, it inhibited the electrically induced tachycardic response (50% inhibition at 0.10 μ g/kg) and increased mean arterial pressure (50 mmHg at 0.23 μ g/kg). Compound showed analgesic activity in the rat tail-flick test (ED_{50} = 0.7 μ g/rat i.t.) and weak sedative potency (ED_{50} = 30 μ g/rat i.t.), giving a sedation/analgesia ratio (43) higher than the reference compound clonidine (0.8). Potentially useful as a spinal analgesic for clinical use.

SOURCE – Orion Corporation.

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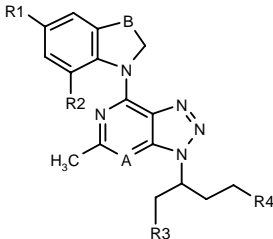
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4. Xu, M. et al. *The effects of MPV-2426, a novel α_2 -adrenergic agonist in different pain models*. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 520.

*Identified compound **251317** (see **251161**) Drug Data Report 1997, 019(07): 0664.

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist claimed for the treatment of a broad range of disorders including affective disorder, anxiety, depression, headache, posttraumatic stress disorder, supranuclear palsy, epilepsy, stroke, irritable bowel syndrome, immune suppression, Alzheimer’s disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, cardiovascular disorders, obesity or fertility disorders. Other specifically claimed compounds from this series of heterocyclyl-substituted ring-fused pyridines and pyrimidines include the following:



Compound	R1	R2	R3	R4	A	B	Formula
275145	Et	Cl	Me	OMe	N	-CH2-	C ₂₁ H ₂₇ ClN ₆ O
275146	SO2Me	Cl	Me	OMe	N	-CH2-	C ₂₀ H ₂₅ ClN ₆ O ₃ S
275147	Br	Br	OMe	OMe	CH	-CH2-	C ₂₀ H ₂₃ Br ₂ N ₅ O ₂
275148	OMe	Cl	OMe	H	CH	-CH2-	C ₂₀ H ₂₄ ClN ₅ O ₂
275150	SO2Me	Cl	Me	H	CH	-CH2-	C ₂₀ H ₂₄ ClN ₅ O ₂ S
275151	Cl	Cl	CH2OMe	OMe	CH	-CH2-	C ₂₁ H ₂₅ Cl ₂ N ₅ O ₂
275152	CN	Cl	Me	H	CH	-CH2-	C ₂₀ H ₂₁ ClN ₆
275153	Me	Cl	Me	H	CH	-(CH2)2-	C ₂₁ H ₂₆ ClN ₅
275154	Ac	Cl	Me	H	CH	-(CH2)2-	C ₂₂ H ₂₆ ClN ₅ O

SOURCE – DuPont Pharmaceuticals.

REFERENCES

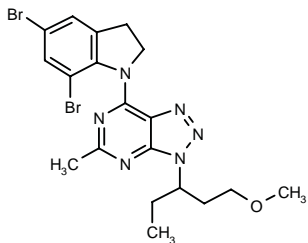
1. Arvanitis, A.G. et al. (DuPont Pharmaceuticals Co.) *Heterocyclyl-substd. ring-fused pyridines and pyrimidines as corticotropin releasing hormone (CRH) antagonists, useful for treating CNS and stress-related disorders*. WO 9911643.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

275144

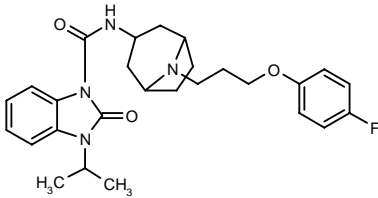
7-(5,7-Dibromo-2,3-dihydro-1*H*-indol-1-yl)-3-(1-ethyl-3-methoxypropyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine



C19 H22 Br2 N6 O; Mol wt: 510.2318

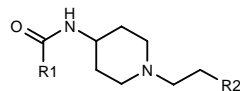
275776

N-[8-[3-(4-Fluorophenoxy)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide



C27 H33 F N4 O3; Mol wt: 480.5807

ACTION – Agent with high affinity and selectivity for 5-HT₄ receptors potentially useful for the treatment or prophylaxis of disorders such as anxiety, pain, depression, schizophrenia, memory disorders, dementia, gastrointestinal disorders such as irritable bowel syndrome, nausea, gastroesophageal reflux disease, dyspepsia, gastrointestinal motility disorders and constipation, cardiovascular disorders such as atrial fibrillation, arrhythmias and tachycardia, and genitourinary disorders such as urinary retention, urinary incontinence and pain on urination. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
275777	3-i-Pr-2-oxo-2,3-dihydro-1-benzimidazolyl	4-F-PhOCH2	C ₂₅ H ₃₁ FN ₄ O ₃
275778	1-i-Pr-3-indazolyl	4-F-PhOCH2	C ₂₅ H ₃₁ FN ₄ O ₂
275779	1-i-Pr-3-indazolyl	1,3-dioxo-2-isoindoliny	C ₂₆ H ₂₉ N ₅ O ₃
275780	1-i-Pr-3-indazolyl	NHSO2Me	C ₁₉ H ₂₉ N ₅ O ₃ S
275781	1-i-Pr-3-indazolyl	NHCOPh	C ₂₅ H ₃₁ N ₅ O ₂
275782	1-i-Pr-3-indazolyl	1-adamantyl-CONH	C ₂₉ H ₄₁ N ₅ O ₂

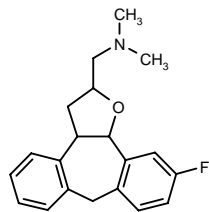
SOURCE – Lilly.

REFERENCES

1. Cohen, M.L. et al. (Eli Lilly and Company) 5HT₄ agonists and antagonists. EP 908459, WO 9917772.

275999

N-(11-Fluoro-3,3a,8,12b-tetrahydro-2H-dibenzo[3,4:6,7]-cyclohepta[1,2-b]furan-2-ylmethyl)-N,N-dimethylamine



C20 H22 F N O; Mol wt: 311.3978

ACTION – Agent for the treatment of anxiety, depression, schizophrenia, migraine and drug addiction with affinity for 5-HT₂ receptors, particularly 5-HT_{2A} and 5-HT_{2C} receptors, reported to be more chemically stable and to have a faster onset of action compared to structurally related compounds. *In vivo*, compound is reported to suppress mCPP-induced hypolocomotion in rats and to antagonize the central symptoms induced by apomorphine and tryptamine. A specifically claimed compound from a series of halogen-substituted tetracyclic tetrahydrofuran derivatives.

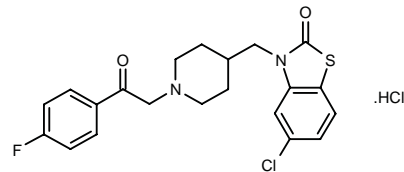
SOURCE – Janssen.

REFERENCES

1. Andrés-Gil, J.I. et al. (Janssen Pharmaceutica NV) Halogen subst. tetracyclic tetrahydrofuran derivs. WO 9919317.

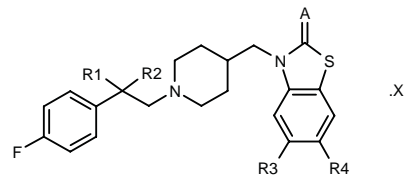
277641

5-Chloro-3-[1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-ylmethyl]benzothiazol-2(3H)-one hydrochloride



C21 H20 Cl F N2 O2 S . HCl ; Mol wt: 455.3789

ACTION – Agent with high affinity for σ-receptors (K_i = 3.1 nM vs. 29 nM for haloperidol), potentially useful in the treatment of CNS disorders such as anxiety, depression, schizophrenia, drug abuse and withdrawal, pain, dyskinesia, epilepsy, Alzheimer's disease, Parkinson's disease and attention deficit disorder, gastrointestinal disorders such as irritable bowel syndrome and cardiovascular disorders such as hypertension, arrhythmia and angina pectoris. A representative compound from a series of alkylamino derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	X	Formula
277642	-O-		H	Cl	-N(Me)-	2HCl	C ₂₂ H ₂₃ Cl ₂ FN ₃ OS.2HCl
277643	-O-		H	Br	-O-	HCl	C ₂₁ H ₂₀ BrFN ₂ O ₂ S.HCl
277644	OH	H	H	Br	-O-	HCl	C ₂₁ H ₂₂ BrFN ₂ O ₂ S.HCl
277645	-O-		H	Cl	-O-	HCl	C ₂₁ H ₂₀ FN ₂ O ₂ S.HCl
277646	OH	H	Cl	H	-O-	HCl	C ₂₁ H ₂₂ ClFN ₂ O ₂ S.HCl

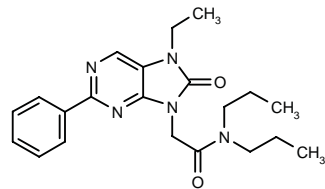
SOURCE – Mitsubishi Chemical.

REFERENCES

1. Rocher, J.-P. et al. (Mitsubishi Chemical Corp.) Novel alkylamino derivs. JP 99217377, WO 9923083.

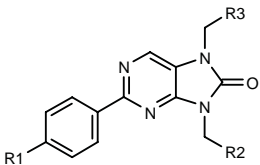
278501

2-(7-Ethyl-8-oxo-2-phenyl-8,9-dihydro-7H-purin-9-yl)-N,N-dipropylacetamide



C21 H27 N5 O2; Mol wt: 381.4773

ACTION – Anxiolytic agent and anticonvulsant with high affinity for the peripheral benzodiazepine site of the GABA_A receptor (IC₅₀ = 0.66 nM in a binding assay). It gave a minimum effective dose (MED) of 0.001 mg/kg p.o. in the light/dark box test for anxiolytic activity in mice and an ED₂₅ of 33.0 mg/kg p.o. against isoniazid-induced clonic seizures in mice. Other exemplified 2-aryl-8-oxo-dihydropurine derivatives include the following:



Compound	R1	R2	R3	Formula
278502	H	H	CON(Et)Ph	C ₂₂ H ₂₁ N ₅ O ₂
278503	H	H	CON(Me)Ph	C ₂₁ H ₁₉ N ₅ O ₂
278504	F	H	CON(Me)Ph	C ₂₁ H ₁₈ FN ₅ O ₂
278506	H	CON(Pr)2	H	C ₂₀ H ₂₆ N ₅ O ₂
278507	Cl	CON(Me)CH ₂ Ph	H	C ₂₂ H ₂₀ ClN ₅ O ₂
278508	Cl	CON(Et)CH ₂ Ph	H	C ₂₃ H ₂₂ ClN ₅ O ₂

SOURCE – Dainippon Pharmaceutical.

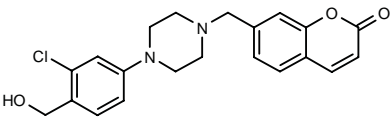
REFERENCES

1. Murata, T. et al. (Dainippon Pharmaceutical Co., Ltd.) 2-Aryl-8-oxodihydropurine derivs., process for producing the same, medicinal compsns. containing the same, and intermediates thereof. WO 9928320.

ANTIPSYCHOTIC DRUGS

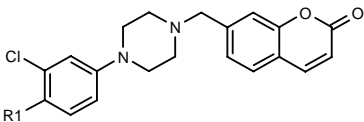
278462

7-[4-[3-Chloro-4-(hydroxymethyl)phenyl]piperazin-1-ylmethyl]-1-benzopyran-2-one

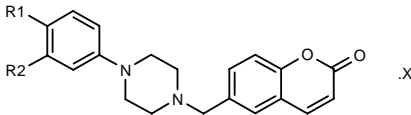


C21 H21 Cl N2 O3; Mol wt: 384.8609

ACTION – Dopamine D₄ receptor antagonist for the treatment of schizophrenia and other psychoses. It exhibits high affinity and selectivity for dopamine D₄ receptors relative to dopamine D₂ receptors (K_i = 11 and 10,565 nM, respectively, in a binding assay). Other exemplified coumarin derivatives include the following:



Compound	R1	Formula
278463	Me	C ₂₁ H ₂₁ ClN ₂ O ₂
278464	H	C ₂₀ H ₁₉ ClN ₂ O ₂
278465	CHO	C ₂₁ H ₁₉ ClN ₂ O ₃



Compound	R1	R2	R3	Formula
278466	CH ₂ OH	Cl		C ₂₁ H ₂₁ ClN ₂ O ₃
278467	H	H	HCl	C ₂₀ H ₂₀ N ₂ O ₂ .HCl

SOURCE – Warner-Lambert.

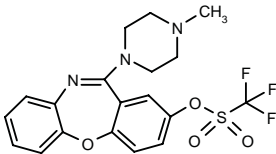
REFERENCES

1. Johnson, S.J. et al. (Warner-Lambert Co.) Coumarin dopamine D₄ receptor antagonists. US 5922719.

GMC2-83*1-3

242893

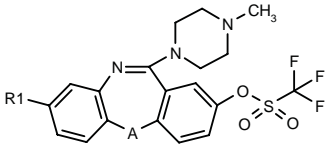
11-(4-Methylpiperazin-1-yl)-2-(trifluoromethanesulfonyloxy)dibenzo[b,f][1,4]oxazepine



C19 H18 F3 N3 O4 S; Mol wt: 441.4320

M.p. 117-8 °C.

ACTION – Atypical antipsychotic agent with a multi-receptor binding profile comparable to that of clozapine, but without anticholinergic properties. Compound showed high affinity for rat dopamine D₁ and D₂ and human D₂ and D₃ receptors (K_i = 66, 40, 52 and 29 nM, respectively), 5-HT_{2A} and 5-HT_{2C} receptors (K_i = 48 and 100 nM, respectively) and α₁ adrenoceptors (K_i = 27 nM), but low affinity for cholinergic muscarinic M₁ receptors (IC₅₀ = 490 nM). Compound increased *ex vivo* L-DOPA accumulation in rat striatum with an ED₅₀ of 0.7 mg/kg p.o. In behavioral studies, orally administered drug strongly inhibited apomorphine-induced climbing in mice (ED₅₀ = 1.3 mg/kg p.o.) at doses with low cataleptogenic activity (ED₅₀ = 28 mg/kg p.o.), giving a favorable therapeutic ratio (21.5) when compared to haloperidol, isoclozapine or clozapine (5.5. 1.1 and > 5.8, respectively). Other related piperazinylidibenzazepines include the following:



Compound	R1	A	Formula
GMC3-06 [242895]**1,3	H	S	C ₁₉ H ₁₈ F ₃ N ₃ O ₃ S ₂
GMC61-39 [277700] ³	Cl	NH	C ₁₉ H ₁₈ ClF ₃ N ₄ O ₃ S

SOURCES – Lundbeck; Merck KGaA.

REFERENCES

1. Wikström, H. et al. New sulfone analogues of iso-clozapine and related structures: Atypical neuroleptics. WO 9629316.
2. Alves-Rodrigues, A. et al. Binding of clozapine metabolites and analogues to the histamine H₃ receptor in rat brain cortex. Arch Pharm 1996, 329(8-9): 413.

3. Liao, Y. et al. *New (sulfonyloxy)piperazinyldibenzazepines as potential atypical antipsychotics: Chemistry and pharmacological evaluation.* J Med Chem 1999, 42(12): 2235.

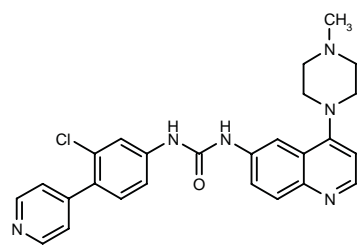
*Identified compound **242893** (see **242168**) Drug Data Report 1997, 019(02): 0114.

Identified compound **242895 (see **242168**) Drug Data Report 1997, 019(02): 0114.

TREATMENTS FOR MOOD DISORDERS

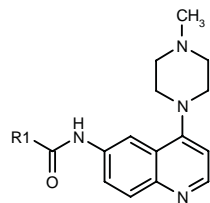
278056

N-[3-Chloro-4-(pyridin-4-yl)phenyl]-*N*'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]urea

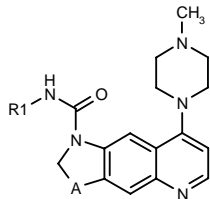


C26 H25 Cl N6 O; Mol wt: 472.9775

ACTION – Combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist with pK_i values > 8.5, potentially useful for the treatment of CNS disorders, particularly depression. Other compounds from this series of quinolinepiperidine and quinolinepiperazine derivatives include the following:



Compound	R1	Formula
278057	4-(4-Pyr)-1-Naph-NH	C ₃₀ H ₂₈ N ₆ O
278058	5-Br-1-Naph-CH2	C ₂₆ H ₂₅ BrN ₄ O
278059	3-CF3-4-(4-Pyr)-PhNH	C ₂₇ H ₂₅ F ₃ N ₆ O
278060	2,3-(Cl)2-PhCH2	C ₂₂ H ₂₂ Cl ₂ N ₄ O
278061	5-(6-Me-3-Pyr)-1-Naph-NH	C ₃₁ H ₃₀ N ₆ O



Compound	R1	A	Formula
278062	4-(4-Pyr)-1-Naph	-CH2-	C ₃₂ H ₃₀ N ₆ O
278063	5-oxo-5,6,7,8-tetrahydro-2-Naph	-(CH2)2-	C ₂₈ H ₃₁ N ₆ O ₂

SOURCE – SmithKline Beecham.

REFERENCES

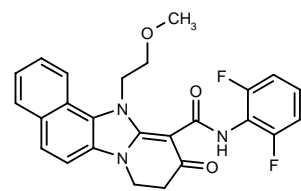
1. Gaster, L.M. (SmithKline Beecham plc) *Quinolinepiperazine and quinolinepiperidine derivs., their preparation and their use as combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonists.* WO 9931086.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

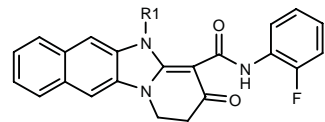
275855

N-(2,6-Difluorophenyl)-12-(2-methoxyethyl)-10-oxo-8,9,10,12-tetrahydronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-11-carboxamide



C25 H21 F2 N3 O3; Mol wt: 449.4549

ACTION – Agent with high affinity for the benzodiazepine binding site on GABA_A receptors, as demonstrated in a binding assay using [³H]-flunitrazepam as the radioligand (IC₅₀ = 0.29 nM), with potential as a muscle relaxant, sedative, anxiolytic, anticonvulsant and antiepileptic agent and for managing alcoholism and drug overdose. Anticonvulsant activity was demonstrated by inhibition of pentylenetetrazol-induced convulsions in mice (ED₅₀ = 1 mg/kg i.p.). Other compounds within this series of naphthoimidazo[1,2-*a*]pyridine derivatives include the following:



Compound	R1	Formula
275856	Et	C ₂₄ H ₂₀ FN ₃ O ₂
275857	CH2CH2OMe	C ₂₈ H ₂₂ FN ₃ O ₃

SOURCE – Ortho-McNeil.

REFERENCES

1. Reitz, A.B. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Naphtho-imidazo[1,2-a]pyridine derivs., their preparation and their use in treating central nervous system disorders.* WO 9918104.

3. Liao, Y. et al. *New (sulfonyloxy)piperazinyldibenzazepines as potential atypical antipsychotics: Chemistry and pharmacological evaluation.* J Med Chem 1999, 42(12): 2235.

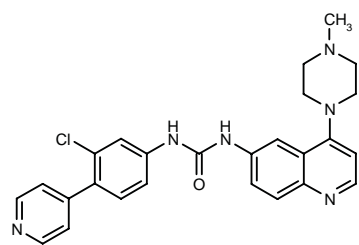
*Identified compound **242893** (see **242168**) Drug Data Report 1997, 019(02): 0114.

Identified compound **242895 (see **242168**) Drug Data Report 1997, 019(02): 0114.

TREATMENTS FOR MOOD DISORDERS

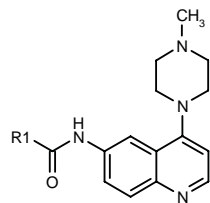
278056

N-[3-Chloro-4-(pyridin-4-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]urea

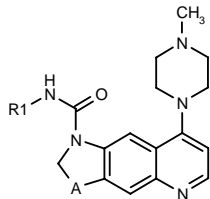


C26 H25 Cl N6 O; Mol wt: 472.9775

ACTION – Combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist with pK_i values > 8.5, potentially useful for the treatment of CNS disorders, particularly depression. Other compounds from this series of quinolinepiperidine and quinolinepiperazine derivatives include the following:



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278059	3-CF3-4-(4-Pyr)-PhNH	C ₂₇ H ₂₅ F ₃ N ₆ O
278060	2,3-(Cl)2-PhCH2	C ₂₂ H ₂₂ Cl ₂ N ₄ O
278061	5-(6-Me-3-Pyr)-1-Naph-NH	C ₃₁ H ₃₀ N ₆ O



Compound	R1	A	Formula
278062	4-(4-Pyr)-1-Naph	-CH2-	C ₃₂ H ₃₀ N ₆ O
278063	5-oxo-5,6,7,8-tetrahydro-2-Naph	-(CH2)2-	C ₂₈ H ₃₁ N ₆ O ₂

SOURCE – SmithKline Beecham.

REFERENCES

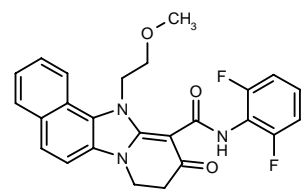
1. Gaster, L.M. (SmithKline Beecham plc) *Quinolinepiperazine and quinolinepiperidine derivs., their preparation and their use as combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonists.* WO 9931086.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

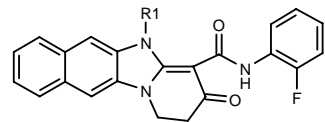
275855

N-(2,6-Difluorophenyl)-12-(2-methoxyethyl)-10-oxo-8,9,10,12-tetrahydronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-11-carboxamide



C25 H21 F2 N3 O3; Mol wt: 449.4549

ACTION – Agent with high affinity for the benzodiazepine binding site on GABA_A receptors, as demonstrated in a binding assay using [³H]-flunitrazepam as the radioligand (IC₅₀ = 0.29 nM), with potential as a muscle relaxant, sedative, anxiolytic, anticonvulsant and antiepileptic agent and for managing alcoholism and drug overdose. Anticonvulsant activity was demonstrated by inhibition of pentylenetetrazol-induced convulsions in mice (ED₅₀ = 1 mg/kg i.p.). Other compounds within this series of naphthoimidazo[1,2-*a*]pyridine derivatives include the following:



Compound	R1	Formula
275856	Et	C ₂₄ H ₂₀ FN ₃ O ₂
275857	CH2CH2OMe	C ₂₅ H ₂₂ FN ₃ O ₃

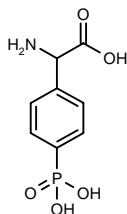
SOURCE – Ortho-McNeil.

REFERENCES

1. Reitz, A.B. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Naphtho-imidazo[1,2-*a*]pyridine derivs., their preparation and their use in treating central nervous system disorders.* WO 9918104.

277385

(±)-2-Amino-2-(4-phosphonophenyl)acetic acid



C8 H10 N O5 P; Mol wt: 231.1430

ACTION – Anticonvulsant and neuroprotective agent, a potent and selective human group III metabotropic glutamate receptor (mgluR) agonist, as demonstrated in recombinant cells stably expressing human mgluR subtypes such as mglu_{8a}, mglu_{4a}, mglu₆ and mglu_{7b} (IC₅₀ = 0.2, 5.2, 4.7 and 185 μM, respectively). Compound also showed micromolar affinity for the Ca²⁺/Cl⁻-dependent L-[³H]-glutamate binding site (IC₅₀ = 1.9 μM), but did not significantly inhibit group I and group II human mgluR (IC₅₀ > 200 μM) and was inactive against human NMDA, AMPA and kainate receptors. It exhibited neuroprotective activity against NMDA-induced toxicity in cultured mouse cortical neurons (EC₅₀ = 12 μM) and protected against NMDA- and quinolinic acid-induced striatal lesions in rats (100 and 58.4% protection, respectively, at 250 nmol infused into striatum). Anticonvulsant activity was observed in the maximal electroshock model in mice (ED₅₀ = 78 nmol i.c.v.), with no proconvulsant effect up to 2200 nmol i.c.v.

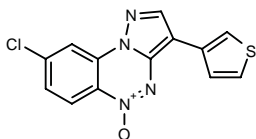
SOURCES – Novartis; Sibia Neurosciences.**REFERENCES**

1. Bigge, C.F. et al. *Exploration of phenyl-spaced 2-amino-(5-9)-phosphonoalkanoic acids as competitive N-methyl-D-aspartic acid antagonists*. J Med Chem 1989, 32(7): 1580.

2. Gasparini, F. et al. *(R,S)-4-Phosphonophenylglycine, a potent and selective group III metabotropic glutamate receptor agonist, is anticonvulsive and neuroprotective in vivo*. J Pharmacol Exp Ther 1999, 289(3): 1678.

277699

8-Chloro-3-(3-thienyl)pyrazolo[5,1-c][1,2,4]benzotriazine-5-oxide



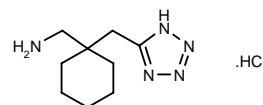
C13 H7 Cl N4 O S; Mol wt: 302.7443

M.p. 220-1 °C.

ACTION – High-affinity ligand for the benzodiazepine site on the GABA_A receptor (K_i = 36.3 nM for inhibition of [³H]-flumazenil binding in bovine brain membranes) with selective anticonvulsant activity *in vivo* in mice; it significantly prevented convulsions induced by both pentylenetetrazol (61.5 and 46.1%, respectively, at 30 and 100 mg/kg p.o.) and maximal electroshock (33.3% protection at 30 mg/kg p.o.), with no significant muscle relaxant or anxiolytic activity.

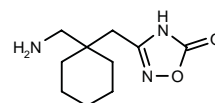
SOURCES – Università degli Studi di Firenze, Firenze (IT); Università degli Studi di Pisa, Pisa (IT).**REFERENCES**

1. Costanzo, A. et al. *Benzodiazepine receptor ligands. 4. Synthesis and pharmacological evaluation of 3-heteroaryl-8-chloropyrazolo[5,1-c][1,2,4]benzotriazine 5-oxides*. J Med Chem 1999, 42(12): 2218.

277952[1-(1*H*-Tetrazol-5-ylmethyl)cyclohexyl]methylamine hydrochloride

C9 H17 N5 . HCl; Mol wt: 231.7292

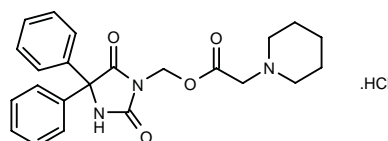
ACTION – Anticonvulsant also useful in the treatment of other neurological and CNS disorders including faintness attacks, hypokinesia, neurodegenerative disorders, depression, anxiety, panic and pain. It shows good binding affinity for the Ca²⁺ channel α2-δ subunit and is thus expected to have similar pharmacological effects to gabapentin. It had an IC₅₀ in the α2-δ receptor binding assay of 0.203 nM (gabapentin = 0.14 nM), and it was highly active in the audiogenic seizure model in DBA/2 mice at 10 mg/kg p.o., providing 60, 100, 100 and 80% protection, respectively, at 1, 2, 4 and 6 h postdosing. Another representative compound from this series of gabapentin analogues is:

**277953:** C10 H17 N3 O2**SOURCE** – Warner-Lambert.**REFERENCES**

1. Bryans, J.S. et al. (Warner-Lambert Co.) *1-Substd.-1-aminomethyl-cycloalkane derivs. (=gabapentin analogues), their preparation and their use in the treatment of neurological disorders*. WO 9931075.

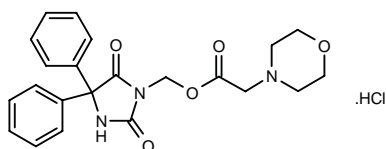
278083²

2-(1-Piperidiny)acetic acid 2,5-dioxo-4,4-diphenylimidazolidin-1-ylmethyl ester hydrochloride



C23 H25 N3 O4 . HCl; Mol wt: 443.9284

ACTION – Water-soluble phenytoin prodrug that is hydrolyzed very quickly in whole blood, reaching 97% hydrolysis in 5 min compared to about 10% for fosphenytoin at this time point. Potentially useful as an anticonvulsant agent for the therapy of epilepsy, as well as an antiarrhythmic agent. Another related compound is:



278084^{1,2}: C22 H23 N3 O5 . HCl

SOURCE – Universitat de Barcelona, Barcelona (ES).

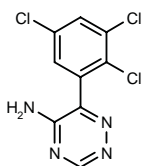
REFERENCES

1. Roca Estrem, T. et al. (Laboratorios Rubio, SA) *Prodrugs of 5,5-diphenylhydantoin as antiepileptic and antiarrhythmic agents*. EP 693481.

2. Bosch, J. et al. *Synthesis of water-soluble phenytoin prodrugs*. Bioorg Med Chem Lett 1999, 9(13): 1859.

278355

6-(2,3,5-Trichlorophenyl)-1,2,4-triazin-5-amine



C9 H5 Cl3 N4; Mol wt: 275.5255

ACTION – Voltage-dependent sodium channel blocker with potent anticonvulsant activity, reported to be more potent than lamotrigine and to show increased selectivity in terms of CNS side effects and inhibition of dihydrofolate reductase. It is therefore useful for the treatment of CNS disorders such as epilepsy, as well as manic depression (bipolar disorder), pain, functional bowel disorders, neurodegenerative disorders, tinnitus and drug dependence. In preliminary biological testing, the compound gave an ED₅₀ of 1.7 mg/kg p.o. in the rat maximal electroshock seizure (MES) test compared to 6.1 mg/kg p.o. for lamotrigine, and it also showed a much higher therapeutic index than the reference compound (ED₅₀ ataxia/ED₅₀ MES = 23.7 vs. 3.3); the compound was also more potent than lamotrigine in the pentylenetetrazol seizure test in mice (ED₅₀ = 3.8 mg/kg vs. 8.4 mg/kg). Furthermore, significant antiinflammatory and analgesic activity was observed in the carrageenan-induced paw hyperalgesia and inflammation model, and it provided significant protection against MPTP-induced striatal dopamine depletion in mice.

SOURCE – Glaxo Wellcome.

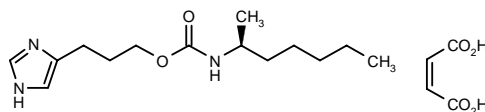
REFERENCES

1. Cox, B. et al. (Glaxo Group Ltd.) *Triazine cpds. for treatment of CNS disorders*. WO 9932462.

COGNITION-ENHANCING DRUGS

277055

N-[1(*S*)-Methylhexyl]carbamic acid 3-(1*H*-imidazol-4-yl)-propyl ester fumarate



C14 H25 N3 O2 . C4 H4 O4; Mol wt: 383.4421

M.p. 115 °C, [α]_D²⁰ +2.43° (*c* 1.00, EtOH).

ACTION – Potent and selective, centrally acting histamine H₃ receptor antagonist (K_i = 18 nM in rat cerebral cortex synaptosomes) with the ability to strongly enhance brain histamine turnover in mice (ED₅₀ = 0.39 mg/kg i.p.), being 2.5-fold more potent than thioperamide. Potentially useful for the treatment of H₃ receptor-mediated CNS disorders such as epilepsy, schizophrenia, arousal and sleep disorders, eating and drinking behavior, memory and learning deficits and Alzheimer's disease.

SOURCES – Bioprojet; INSERM.

REFERENCES

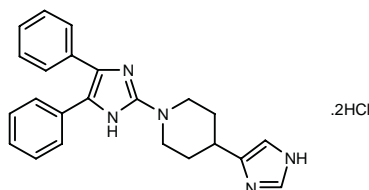
1. Schwartz, J.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) *Imidazole derivs. as histamine receptor H3 (ant)agonists*. EP 760811, FR 2732017, JP 98501001, WO 9629315.

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3. Sasse, A. et al. *Development of chiral N-alkylcarbamates as new leads for potent and selective H3-receptor antagonists: Synthesis, capillary electrophoresis, and in vitro and oral in vivo activity*. J Med Chem 1999, 42(4): 593.

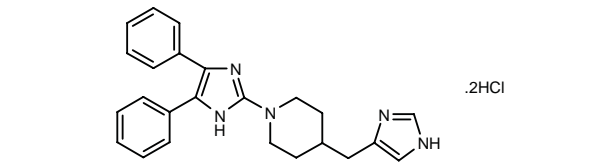
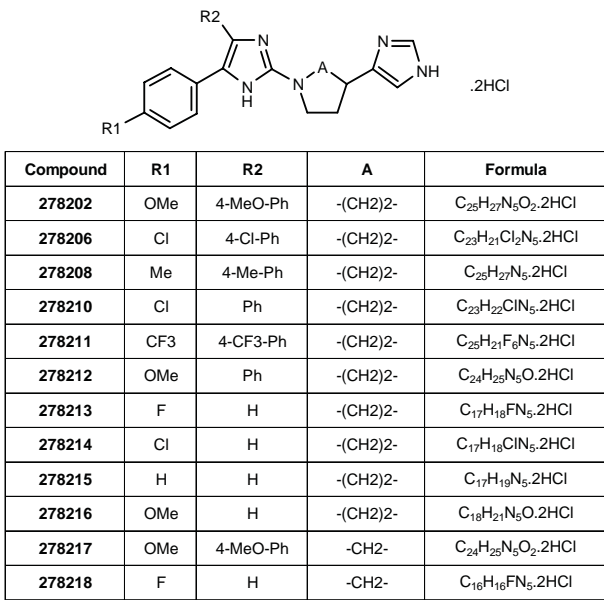
278201

1-(4,5-Diphenyl-1*H*-imidazol-2-yl)-4-(1*H*-imidazol-4-yl)piperidine dihydrochloride



C23 H23 N5 . 2HCl; Mol wt: 442.3915

ACTION – Agent for the treatment of CNS disorders including Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, sexual dysfunction, sleep disorders, migraine and epilepsy, as well as hypertension, inflammatory disorders, asthma and allergy, that possesses affinity for histamine H₃ receptors. Other compounds from this series of 1-(1*H*-imidazol-2-yl)pyrrolidine and 1-(1*H*-imidazol-2-yl)piperidine derivatives include the following:



278219: C₂₄ H₂₅ N₅. 2HCl

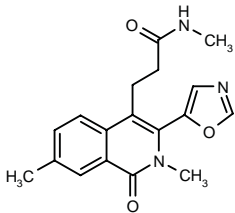
SOURCE – Sanofi-Synthélabo.

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1. Jegham, S. et al. (Sanofi SA) 1-(1*H*-imidazol-2-yl)pyrrolidine and 1-(1*H*-imidazol-2-yl)piperidine) derivs., preparation and therapeutic application. FR 2772377, WO 9931089.

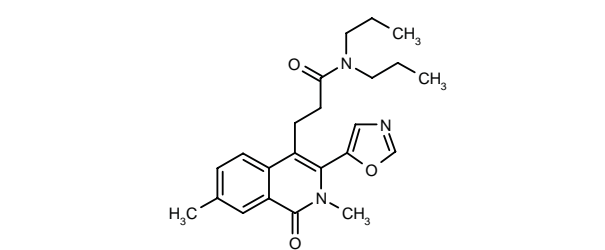
278414

3-[2,7-Dimethyl-3-(oxazol-5-yl)-1-oxo-1,2-dihydroisoquinolin-4-yl]-*N*-methylpropanamide



C₁₈ H₁₉ N₃ O₃; Mol wt: 325.3661

ACTION – GABA_A/benzodiazepine receptor complex modulator with high affinity for GABA_A receptors containing α3 and/or α5 subunits, and weaker affinity for receptors containing the α1 or α2 and α3 subunits. Potentially useful in the treatment of anxiety, depression, sleep disorders, epilepsy, spasticity and muscle contractions, and particularly olfactory and cognitive disorders, hormonal disorders associated with hypothalamic dysfunction, certain affective disorders and pain perception. Another exemplified 3-oxazol-5-yl-1-oxo-1,2-dihydroisoquinoline-4-propanamide derivative is:



278415: C₂₃ H₂₉ N₃ O₃

SOURCE – Sanofi-Synthélabo.

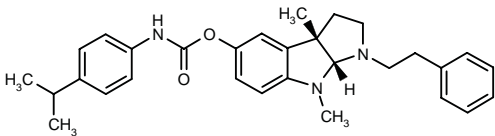
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1. Marabout, B. et al. (Sanofi Pharmaceuticals, Inc.) 3-Oxazol-5-yl-1-oxo-1,2-dihydroisoquinoline-4-propanamide derivs., preparation and therapeutic application. FR 2772760, WO 9932485.

N¹-PHENETHYLNORCYMSERINE^{2,5}

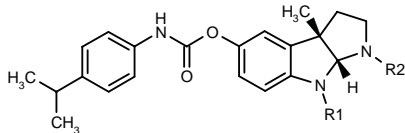
276191

N-(4-Isopropylphenyl)carbamic acid (3a*S*,8a*R*)-3a,8-dimethyl-1-(2-phenylethyl)-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indol-5-yl ester



C₃₀ H₃₅ N₃ O₂; Mol wt: 469.6255

ACTION – Potent, selective and reversible human butyrylcholinesterase (BChE) inhibitor (IC₅₀ = 6 nM in human plasma) with > 5000-fold selectivity over acetylcholinesterase (AChE) and being 8-fold more potent and 1250-fold more selective than tacrine. Compound was well tolerated *in vivo*, was able to pass through the blood–brain barrier and improved cognitive performance in rodents. Potentially useful for the treatment of Alzheimer’s disease. Other cymserine derivatives include the following:



Compound	R1=R2	Formula
Cymserine [269466] ¹⁻⁵	Me	C ₂₃ H ₃₁ N ₃ O
N1,N8-Bisnorcymserine [276192] ^{2,5}	H	C ₂₁ H ₂₅ N ₃ O ₂

SOURCES – Axonyx; National Institutes of Health, Bethesda, MD (US).

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2. Greig, N.H. et al. (National Institutes of Health;Axonyx Inc.) Highly selective butyrylcholinesterase inhibitors for the treatment and diagnosis of Alzheimer’s disease and dementias. CA 2264750, WO 9902154.

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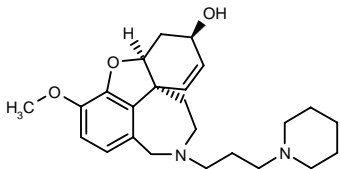
4. Greig, N.H. et al. *Novel, selective butyrylcholinesterase (BChE) inhibitors for the treatment of Alzheimer's disease (AD)*. Soc Neurosci Abst 1998, 24(Part 1): Abst 284.18.

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SPH-1286

278428

(-)-(4a*S*,6*R*,8a*S*)-6-Hydroxy-3-methoxy-11-[3-(piperidin-1-yl)propyl]-5,6,9,10,11,12-hexahydro-4a*H*-benzo-furo[3a,3,2-*e,f*][2]benzazepine



C24 H34 N2 O3; Mol wt: 398.5436

ACTION – Acetylcholinesterase (AChE) inhibitor with affinity for human AChE higher than the parent compound galanthamine (IC₅₀ = 0.3 and 2.3 μM, respectively). In behavioral experiments, compound antagonized both age-related and scopolamine-induced cognitive impairments in rats, prevented carbon dioxide-induced amnesia in rats and antagonized hypoxia-induced memory impairment in mice. In the latter model, complete prevention of amnesia was achieved with a dose of 100 mg/kg p.o. or piracetam at a dose of 300 mg/kg p.o. Potentially useful for the treatment of CNS disorders related to a deficit in cholinergic neurotransmission such as Alzheimer’s disease.

SOURCE – Sanochemia.

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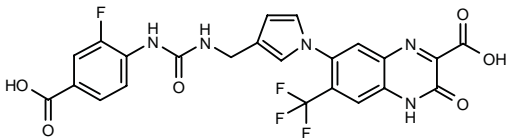
1. Czollner, L. et al. (Sanochemia Ltd.) *New benzazepine derivs., medicaments containing the same and their use to prepare medicaments*. WO 9740049.

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TREATMENT OF Cerebrovascular Diseases

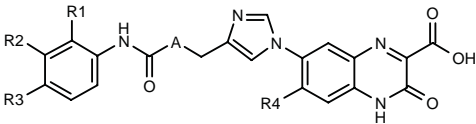
275907

7-[3-[*N*³-(4-Carboxy-2-fluorophenyl)ureidomethyl]-1*H*-pyrrol-1-yl]-3-oxo-6-(trifluoromethyl)-3,4-dihydro-quinoxaline-2-carboxylic acid



C23 H15 F4 N5 O6; Mol wt: 533.3925

ACTION – Neuroprotective agent, a potent AMPA receptor antagonist (K_i = 11.8 nM). Other compounds from this series of quinoxalinecarboxylic acid derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
275908	H	H	CO2H	CF3	O	C ₂₂ H ₁₄ F ₃ N ₅ O ₇
275909	F	H	H	NO2	O	C ₂₀ H ₁₃ FN ₅ O ₇
275910	H	H	CO2H	NO2	O	C ₂₁ H ₁₄ N ₆ O ₉
275911	H	CO2H	H	NO2	O	C ₂₁ H ₁₄ N ₆ O ₉
275912	H	H	CO2H	NO2	NH	C ₂₁ H ₁₅ N ₇ O ₈

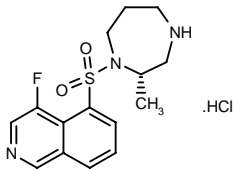
SOURCE – Kyorin.

REFERENCES

1. Takano, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *6,7-Asymmetrically disubstd. quinoxalinecarboxylic acid derivs., addition salts thereof, and processes for the preparation of both*. WO 9911632.

277272

4-Fluoro-5-[2(*S*)-methylperhydro-1,4-diazepin-1-ylsulfonyl]isoquinoline hydrochloride



C15 H18 F N3 O2 S . HCl; Mol wt: 359.8511

ACTION – Cerebral vasodilating and neuroprotective agent with potential in the prevention and treatment of cerebrovascular disorders such as cerebral vasospasm following subarachnoid hemorrhage. Compound was more potent than fasudil hydrochloride in relaxing rat aorta strips contracted with calcium ionophore A23187 (IC₅₀ = 1.7 and 7.4 μM, respectively). *In vivo*, it was also found to exhibit superior vasodilating and neuroprotective properties compared to fasudil hydrochloride in several animal models.

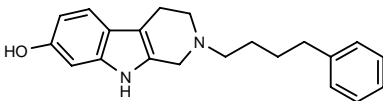
SOURCE – Nippon Shinyaku.

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277393

2-(4-Phenylbutyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-ol



C21 H24 N2 O; Mol wt: 320.4336

ACTION – Potent and selective NMDA receptor antagonist with high selectivity for the NR1A/2B subtype (IC_{50} = 50 nM) over NR1A/2A and NR1A/2C subtypes (IC_{50} = 57 and 67 μ M, respectively). Potentially useful for the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as for acute ischemic cerebrovascular disorders.

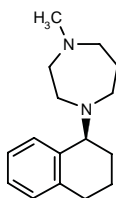
SOURCE – CoCensys.

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278356

(+)-1-Methyl-4-[1,2,3,4-tetrahydronaphthalen-1(S)-yl]-perhydro-1,4-diazepine



C16 H24 N2; Mol wt: 244.3796

ACTION – Neuroprotective agent with selective binding affinity for the [3 H]-emopamil binding site without acting directly at either voltage-sensitive calcium channels (VSCC) or NMDA receptors, and thus exhibiting fewer side effects than emopamil (hypotension) or ifenprodil (behavioral symptoms). It gave an IC_{50} of 17 nM in a [3 H]-emopamil binding assay using guinea pig liver membranes, whereas the value was about 19,000 nM for [3 H]-D-888 binding to L-type VSCC in rat brain cortical membranes. Potentially useful in the treatment of neurodegeneration related to ischemia, i.e., Alzheimer's disease, vascular dementia, AIDS-related dementia, Parkinson's disease and Huntington's disease, and particularly in the treatment of stroke.

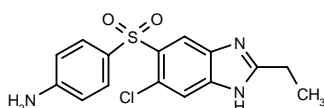
SOURCE – AstraZeneca.

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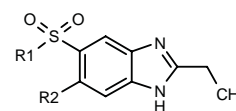
278522

4-(6-Chloro-2-ethyl-1H-benzimidazol-5-ylsulfonyl)aniline



C15 H14 Cl N3 O2 S; Mol wt: 335.8136

ACTION – Neuroprotective agent that acts via inhibition of neuronal apoptosis, as demonstrated against colchicine- or 6-OHDA-induced nerve cell death using human neuroblastoma SH-SY5Y cells. Other representative benzimidazole derivatives are:



Compound	R1	R2	Formula
278523	3-NH2-4-NO2-Ph	Cl	C ₁₅ H ₁₃ ClN ₄ O ₄ S
278524	3,4-(NH2)2-Ph	Cl	C ₁₅ H ₁₅ ClN ₄ O ₂ S
278525	6-quinoxaliny	Cl	C ₁₇ H ₁₃ ClN ₄ O ₂ S
278526	2-Et-6-NO2-5-benzimidazolyl	NO2	C ₁₈ H ₁₆ N ₆ O ₆ S

SOURCE – Snow Brand.

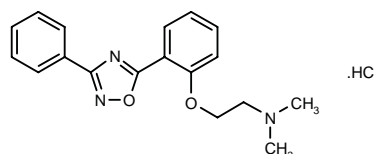
REFERENCES

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BIIR-561-CL

277451

N,N-Dimethyl-*N*-[2-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)-phenoxy]ethyl]amine hydrochloride



C18 H19 N3 O2 . HCl; Mol wt: 345.8280

ACTION – Dual antagonist of AMPA receptors and voltage-dependent sodium channels, shown to inhibit AMPA receptors in a noncompetitive manner with a potency comparable to that of GYKI-52466 under various experimental conditions: it inhibited kainate-, glutamate- and AMPA-mediated membrane currents in rat cortical neurons (IC_{50} = 8.5, 7.6 and 9.3 μ M, respectively), reduced AMPA-induced depolarization in rat cortical wedge preparations (IC_{50} = 10.8 μ M) and did not inhibit the binding of [3 H]-AMPA in rat cortical cell membranes. Compound blocks voltage-gated sodium channels with 10-20-fold greater potency compared to mexiletine: it reduced sodium currents in voltage-clamped cortical neurons with an IC_{50} of 5.2 μ M, inhibited [3 H]-batrachotoxin binding in rat brain synaptosomal membranes with a K_i of 1.2 μ M and inhibited veratridine-induced glutamate release from brain slices with an IC_{50} of 2.3 μ M. *In vivo*, compound suppressed electroshock-induced tonic seizures in mice (ED_{50} = 2.8 mg/kg s.c.) and significantly reduced cortical infarct area in a model of focal cerebral ischemia in mice (44% reduction at 60 mg/kg i.p.). Potentially useful as an anticonvulsant and neuroprotectant.

SOURCE – Boehringer Ingelheim.

REFERENCES

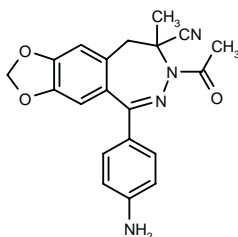
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EGIS-8332

277722

(+)-7-Acetyl-5-(4-aminophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carbonitrile



C20 H18 N4 O3; Mol wt: 362.3872

ACTION – Noncompetitive AMPA/kainate receptor antagonist proven to inhibit kainate-evoked currents in whole-cell patch-clamp experiments and to reduce quisqualate-induced neurotoxicity in primary cultures of embryonic telencephalon cells ($IC_{50} \sim 7 \mu M$). *In vivo*, compound protected against electroshock- and sound-induced seizures with ED_{50} values of 5.5 and 4.6 mg/kg i.p., respectively, with less neurotoxicity compared to GYKI-53405 and GYKI-53655 (minimal toxic dose [MTD] = 100 mg/kg i.p. vs. 30 mg/kg i.p. for reference compounds). It also exhibited neuroprotective effects in a transient bilateral carotid occlusion model in gerbils (67% protection against hippocampal CA1 neuronal death at 20 mg/kg i.p.) and a middle cerebral artery occlusion model of global cerebral ischemia in mice; it increased neuronal survival in the $MgCl_2$ -induced model of global ischemia in mice ($PD_{50} = 19.3$ mg/kg i.p.). Potentially useful for the treatment of acute and chronic neurodegenerative diseases such as stroke, Parkinson's disease and epilepsy.

SOURCE – Egis.

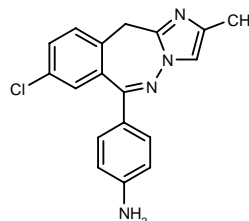
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3. Lévay, G. et al. *Pharmacology of EGIS-8332, a novel non-competitive AMPA antagonist agent.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PS58.
4. Vegh, M. et al. *Inhibition of AMPA/kainate receptors mediated ion channels and cell death by a new 2,3-benzodiazepine derivative EGIS-8332.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PS61.

GYKI-47261*

273541

4-(8-Chloro-2-methyl-11H-imidazo[1,2-c][2,3]benzodiazepin-6-yl)phenylamine



C18 H15 Cl N4; Mol wt: 322.7975

ACTION – Noncompetitive AMPA/kainate receptor antagonist able to attenuate AMPA-induced spreading depression in chicken retina ($IC_{50} = 2.5 \mu M$) and to inhibit AMPA-induced inward currents in Purkinje cells ($IC_{50} = 2.0 \mu M$). *In vivo*, compound showed muscle relaxant activity in the rotarod and inclined screen assays in mice ($ED_{50} = 15.8$ and 36.5 mg/kg i.p., respectively) and antagonized the MPTP-induced dopamine loss and oxotremorine-induced tremor in mice. In a transient middle cerebral artery occlusion model in rats, compound given i.v. at a dose of 1 mg/kg x 6 showed neuroprotective activity, decreasing infarct zone by 62.3%. Potentially useful for the treatment of acute and chronic neurodegenerative diseases such as stroke, Parkinson's disease and epilepsy.

SOURCE – Institute for Drug Research, Budapest (HU).

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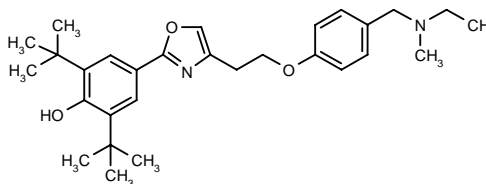
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*Identified compound **273541** Drug Data Report 1999, 021(04): 0311.

LY-341122*

264423

2,6-Di-*tert*-butyl-4-[4-[2-[4-(*N*-ethyl-*N*-methylamino-methyl)phenoxy]ethyl]oxazol-2-yl]phenol



C29 H40 N2 O3; Mol wt: 464.6460

ACTION – Potent inhibitor of lipid peroxidation and free radical scavenger proven to inhibit malondialdehyde production in rat liver microsomes ($IC_{50} = 0.5 \mu M$), reduce LDH production in cultures of rat hippocampal neurons exposed to H_2O_2 (58.3% inhibition at $100 \mu M$) and to inhibit lipid peroxidation *ex vivo* in rat brain. Compound showed neuroprotective effects in rats with moderate brain injury, global and focal ischemic brain damage. In a rat model of parasagittal fluid-percussion brain injury, compound given at a dose of 100 mg/kg 1 h before and 4 h after injury was able to reduce overall contusion volume and contusion area. In a rat model of global cerebral ischemia, compound infused at a dose of 5.0 mg/kg/h induced strong and permanent postischemic protection, as demonstrated by reduction in hippocampal CA1 neuronal damage. In a rat model of focal ischemic brain damage, at doses of 5 or 10 mg/kg/h postischemia it significantly improved neurological scores and reduced total infarct volume.

SOURCE – Lilly.

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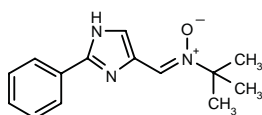
*Identified compound **264423** Drug Data Report 1998, 020(09): 0756.

S-32502-1

277933

N-tert-Butyl-N-(2-phenyl-1H-imidazol-4-ylmethylene)-amine N-oxide

(Z)-N-tert-Butyl-α-(2-phenyl-1H-imidazol-4-yl)nitron



C₁₄ H₁₇ N₃ O; Mol wt: 243.3083

ACTION – Antioxidant active in *in vitro* and *in vivo* models involving oxidative stress, with a potency higher than the reference compound *t*-BPN. Compound prevented L-homocysteic acid-induced neurotoxicity in rat neuronal cultures ($PC_{50} = 88 \mu M$), protected mice against *t*-butylhydroperoxide-induced lethality (60 and 100% survival, respectively, at 150 mg/kg i.p. and 600 mg/kg p.o.) and prevented alloxan-induced hyperglycemia in mice (70-100% protection at 100-600 mg/kg p.o.) at doses lacking hypothermic effects. Potentially useful for the treatment of cerebral ischemia and myocardial infarction.

SOURCE – Servier.

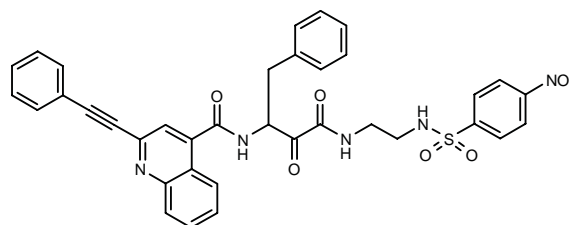
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MISCELLANEOUS NEUROLOGIC DRUGS

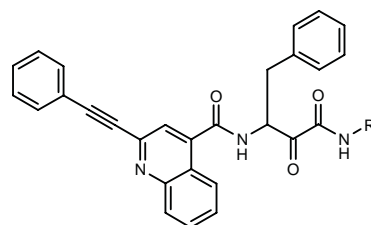
275830

N-[1-Benzyl-3-[2-(4-nitrophenylsulfonamido)ethylamino]-2,3-dioxopropyl]-2-(2-phenylethynyl)quinoline-4-carboxamide



C₃₆ H₂₉ N₅ O₇ S; Mol wt: 675.7191

ACTION – An inhibitor of cysteine and serine proteases such as human calpain I ($IC_{50} = 26 \text{ nM}$), cathepsin B ($IC_{50} = 348 \text{ nM}$) and α -chymotrypsin ($IC_{50} = 14 \text{ nM}$). Potentially useful in the treatment of neurodegenerative and neurotoxic disorders, muscular dystrophy, arthritis, inflammation, myocardial infarction, tumor metastasis, etc. Other representative compounds from this series of quinoline-containing α -ketoamide derivatives include the following:



Compound	R1	Formula
275831	5-(2-Pyr)-2-thienyl-SO ₂ NHCH ₂ CH ₂	C ₃₉ H ₃₁ N ₅ O ₅ S ₂
275832	CH ₂ CH ₂ NHSO ₂ Ph	C ₃₆ H ₃₀ N ₄ O ₅ S
275833	(CH ₂) ₃ NHSO ₂ Ph	C ₃₇ H ₃₂ N ₄ O ₅ S
275834	OE _t	C ₃₀ H ₂₅ N ₅ O ₄
275835	OCH ₂ Ph	C ₃₅ H ₂₇ N ₅ O ₄

SOURCE – Cephalon.

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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

rhuMAb E25

216352

Humanized monoclonal antibody to IgE

E25
Hu-901
IGE-025

ACTION – Antiallergic agent, a recombinant humanized anti-IgE monoclonal antibody that acts by complexing and neutralizing IgE and preventing IgE binding to its high-affinity mast cell receptor. In a phase II clinical trial in pollen-allergic patients, compound (two 300-mg s.c. injections given 3 or 4 weeks apart) decreased the severity of nasal and ocular allergy symptoms and reduced by over 50% the number of rescue allergy medication tablets. In a phase III trial in patients with a history of allergic rhinitis, at a dose of 150 or 300 mg s.c. every 3 or 4 weeks for 12 weeks it improved the rhinitis-related quality of life.

SOURCES – Genentech; Novartis; Tanox.

REFERENCES

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3. Busse, W.W. et al. *A pilot study of the effects of an anti-IgE antibody (E25) on airway inflammation in moderate-severe asthma*. Am J Respir Crit Care Med 1998, 157(3): A456.

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5. Casale, T.B. et al. *Recombinant human monoclonal anti-IgE therapy in allergic rhinitis*. J Allergy Clin Immunol 1996, 97(1, Part 3): Abst 67.

6. Cockcroft, D.W. et al. *rhuMAb-E25 (E25), humanized murine monoclonal anti-IgE, inhibits the allergen-induced early asthmatic response (EAR)*. J Allergy Clin Immunol 1996, 97(1, Part 3): Abst 532.

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12. Fick, R.B. *Anti-IgE therapy*. New Drugs Asthma (June 16-17, London) 1998.

13. Fick, R.B. et al. *Bronchoalveolar lavage fluid (BALF) levels of IgE and an anti-IgE monoclonal antibody (MAb-E) following systemic administration and allergen-induced early asthmatic response (EAR)*. Am J Respir Crit Care Med 1996, 153(4): Abst.

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20. Liu, J. et al. *Thermodynamic analysis of immune complex formation by humanized anti-IgE antibody and IgE*. Pharm Res 1994, 11(10, Suppl.): Abst BIOTEC 2014.

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33. *Tanox tests Hu-901 in peanut allergy*. DailyDrugNews.com (Daily Essentials) 1999, July 19.

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35. Genentech, Inc. Annual Report 1994.

36. Genentech, Inc. Annual Report 1995.

37. Genentech, Inc. Second Quarter Report 1994.

SOURCE – Cephalon.

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RESPIRATORY DRUGS

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216352

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SOURCES – Genentech; Novartis; Tanox.

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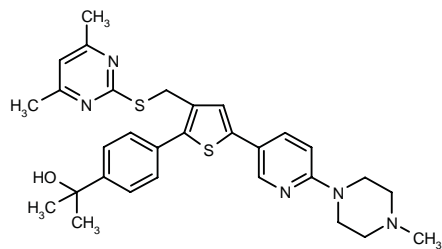
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ASTHMA THERAPY

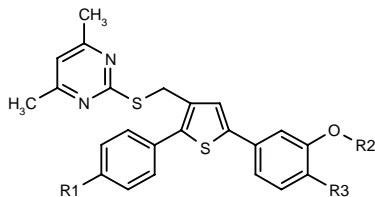
275862

2-[4-[3-(4,6-Dimethylpyrimidin-2-ylsulfanylmethyl)-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]thien-2-yl]phenyl]propan-2-ol

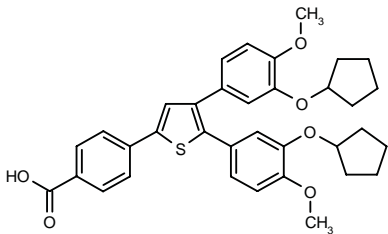


C30 H35 N5 O S2; Mol wt: 545.7725

ACTION – Antiasthmatic agent, a selective phosphodiesterase type 4 (PDE4) inhibitor. Other exemplified compounds from this series of arylthiophene derivatives include the following:



Compound	R1	R2	R3	Formula
275863	CH(Me)2OH	4-Pyr	H	C ₃₁ H ₂₉ N ₃ O ₂ S ₂
275864	CO ₂ H	Me	OMe	C ₂₆ H ₂₄ N ₂ O ₄ S ₂
275865	CH(Me)2OH	Me	OMe	C ₂₈ H ₃₀ N ₂ O ₃ S ₂
275866	1-OH-cyclobutyl	Me	OMe	C ₂₉ H ₃₀ N ₂ O ₃ S ₂
275867	SMe	Me	OMe	C ₂₈ H ₂₆ N ₂ O ₂ S ₃
275868	CH(Me)2OH	H	H	C ₂₆ H ₂₆ N ₂ O ₂ S ₂
275869	CO ₂ H	cyclopentyl	OMe	C ₃₀ H ₃₀ N ₂ O ₄ S ₂



275870: C35 H36 O6 S

SOURCE – Merck Frosst.

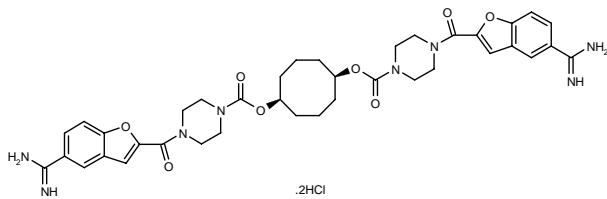
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275935

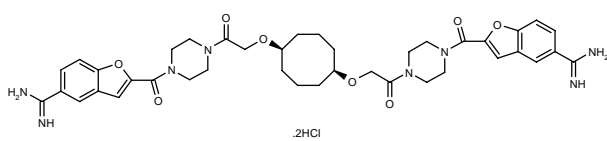
4-(5-Amidinobenzofuran-2-ylcarbonyl)piperazine-1-carboxylic acid diester with *cis*-1,5-cyclooctanediol dihydrochloride

2,2'-(*cis*-Cyclooctane-1,5-diylldioxy)bis(carbonyl)-bis(piperazine-1,4-diyl)bis(carbonyl)bis(benzofuran-5-carboxamide) dihydrochloride

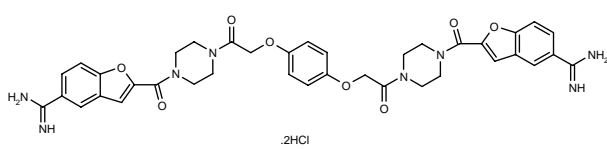


C38 H44 N8 O8 . 2HCl; Mol wt: 813.7354

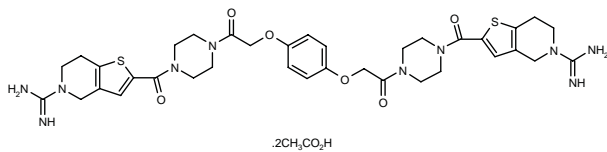
ACTION – Antiallergic agent, an inhibitor of human mast cell tryptase (IC₅₀ = 2.5 pM) with high selectivity relative to other proteases such as thrombin (IC₅₀ = 45 μM). Other exemplified compounds include the following:



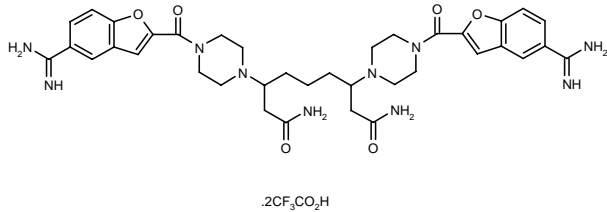
275939: C40 H48 N8 O8 . 2HCl



275940: C38 H38 N8 O8 . 2HCl



275941: C36 H44 N10 O6 S2 . 2C2 H4 O2



275942: C37 H46 N10 O6 . 2C2 H F3 O2

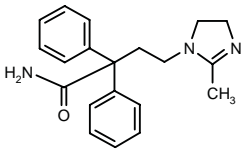
SOURCE – Yoshitomi.

REFERENCES

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276010

4-(2-Methyl-4,5-dihydro-1*H*-imidazol-1-yl)-2,2-diphenylbutyramide



C20 H23 N3 O; Mol wt: 321.4217

ACTION – Muscarinic M₃ receptor antagonist with selectivity for M₃ receptors of the respiratory tract, potentially useful for the treatment of chronic obstructive pulmonary disease and asthma. *In vivo*, it exhibited marked activity in inhibiting methacholine-induced bronchoconstriction in guinea pigs, with ID₅₀ values of 0.3 µg/kg i.v. and 3.3 µg/ml by inhalation, while it showed an ID₅₀ value of 0.9 µg/kg i.v. for inhibition of oxotremorine-induced salivary secretion in the rat.

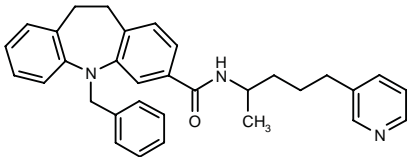
SOURCE – Tokyo Tanabe.

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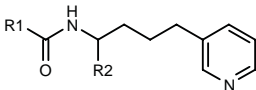
277709

5-Benzyl-*N*-[1-methyl-4-(3-pyridinyl)butyl]-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-3-carboxamide

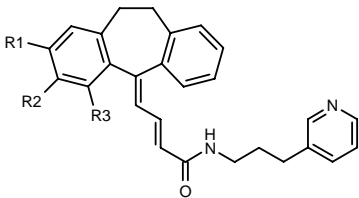


C32 H33 N3 O; Mol wt: 475.6327

ACTION – Antiinflammatory and antiallergic agent, an inhibitor of nitric oxide synthase (NOS), as demonstrated in murine macrophages, where it produced 99% inhibition of lipopolysaccharide (LPS)-stimulated NO production at 10 µM, while showing no cytotoxicity in unstimulated cells. Other compounds from this series of tricyclic derivatives include the following:



Compound	R1	R2	Formula
277793	(E)-10,11-dihydro-5 <i>H</i> -dibenzo-[a,d]cyclohepten-5-ylidene=CHCH=CH	Me	C ₂₉ H ₃₀ N ₂ O
277794	(E)-2,8-(MeO)2-5 <i>H</i> -dibenzo-[a,d]cyclohepten-5-ylidene=CHCH=CH	Me	C ₃₁ H ₃₂ N ₂ O ₃
277796	11-oxo-10,11-dihydro-benzo[<i>b,e</i>]oxepin-3-yl	H	C ₂₄ H ₂₂ N ₂ O ₂
277798	5-oxo-5 <i>H</i> -dibenzo-[a,d]cyclohepten-3-yl	Me	C ₂₆ H ₂₄ N ₂ O ₂
277799	9-(PhCH ₂)-3-carbazolyl	Me	C ₃₀ H ₂₉ N ₃ O



Compound	R1=R2=R3	Formula
277710	H	C ₂₇ H ₂₆ N ₂ O
277792	OMe	C ₃₀ H ₃₂ N ₂ O ₄

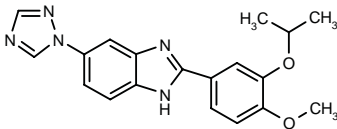
SOURCE – Kyowa Hakko.

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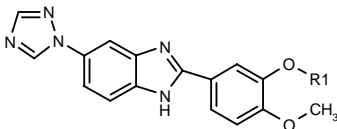
277715

2-(3-Isopropoxy-4-methoxyphenyl)-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-benzimidazole



C19 H19 N5 O2; Mol wt: 349.3921

ACTION – Antiinflammatory and antiallergic agent, an inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.02 µM), also reported to inhibit the production of IL-4 (IC₅₀ = 4.3 µM). *In vivo*, it was found to inhibit ovalbumin-induced ear edema (60% inhibition at 30 mg/kg p.o.), as well as ovalbumin-induced bronchoconstriction (58% inhibition at 10 mg/kg/day p.o. x 10 days) in sensitized mice. Other compounds from this series of benzimidazole derivatives include the following:



Compound	R1	Formula
277716	cyclopentyl	C ₂₁ H ₂₁ N ₅ O ₂
277718	cyclopropyl-CH ₂	C ₂₀ H ₁₉ N ₅ O ₂
277719	2-cyclohexenyl	C ₂₂ H ₂₁ N ₅ O ₂
277721	(E)-CH ₂ CH=CHPh	C ₂₅ H ₂₁ N ₅ O ₂
277723	2-cycloheptenyl	C ₂₃ H ₂₃ N ₅ O ₂

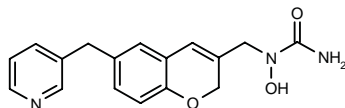
SOURCE – Taiho.

REFERENCES

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277811

*N*¹-Hydroxy-*N*¹-[6-(pyridin-3-yl)methyl]-2*H*-1-benzopyran-3-ylmethyl]urea



C₁₇ H₁₇ N₃ O₃; Mol wt: 311.3393

ACTION – Antiasthmatic agent with dual lipoxygenase- and thromboxane synthase-inhibitory effects. The compound inhibited LTB₄ production in rat polymorphonuclear leukocytes with an IC₅₀ of 0.2 μM and the production of TxB₂ in human platelet microsomes with an IC₅₀ of 0.3 μM. It was also active *ex vivo* in rats following oral administration, giving ED₅₀ values for inhibition of LTB₄ and TxB₂ production of 1.7 and 1.5 mg/kg, respectively. High efficacy was seen against antigen-induced bronchoconstriction in sensitized guinea pigs (75% inhibition at 50 mg/kg p.o.).

SOURCE – Nikken Chemicals.

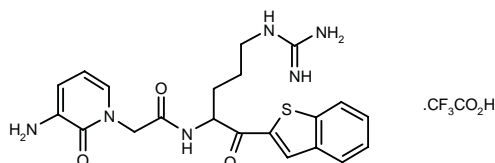
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277904

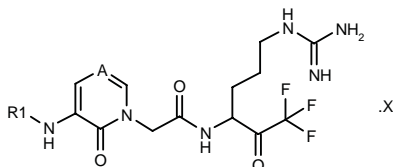
2-(3-Amino-2-oxo-1,2-dihydropyridin-1-yl)-*N*-[1-(1-benzothiophen-2-ylcarbonyl)-4-(guanidino)butyl]acetamide trifluoroacetate

2-[*N*-[2-(3-Amino-2-oxo-1,2-dihydropyridin-1-yl)acetyl]-D,L-arginyl]-1-benzothiophene trifluoroacetate



C₂₁ H₂₄ N₆ O₃ S . C₂ H₃ F₃ O₂; Mol wt: 554.5475

ACTION – Tryptase inhibitor with potent activity against human tryptase (K_i = 15-430 nM) and good selectivity relative to human thrombin. It is thus expected to be useful in the treatment of allergic disorders. Other exemplified heterocyclic amide compounds are:



Compound	R1	A	X	Formula
277905	CO ₂ CH ₂ Ph	N	HCl	C ₂₁ H ₂₄ F ₃ N ₇ O ₅ ·HCl
277906	H	N	2HCl	C ₁₃ H ₁₈ F ₃ N ₇ O ₃ ·2HCl
277907	CO ₂ CH ₂ Ph	CH	HCl	C ₂₂ H ₂₅ F ₃ N ₆ O ₅ ·HCl

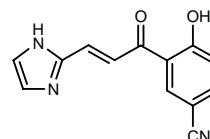
SOURCE – Yoshitomi.

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1. Takeuchi, M. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Tryptase inhibitors comprising heterocyclic amide cpds*. WO 9926925.

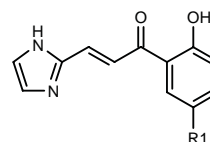
277925

4-Hydroxy-3-[3-(1*H*-imidazol-2-yl)prop-2(*E*)-enoyl]-benzonitrile



C₁₃ H₉ N₃ O₂; Mol wt: 239.2331

ACTION – Cytokine-suppressive agent that inhibits the production of IL-4 (IC₅₀ = 0.26 nM in human T-cells) and is thus expected to have clinical utility as an immune function modulator, and more specifically for diseases such as allergy, atopy and rheumatism, bronchial asthma, IgA nephropathy, osteoporosis, inflammation, cancer and HIV infection, as well as organ transplant rejection. Other exemplified imidazole derivatives include the following:



Compound	R1	Formula
277926	H	C ₁₂ H ₁₀ N ₂ O ₂
277927	Ph	C ₁₈ H ₁₄ N ₂ O ₂

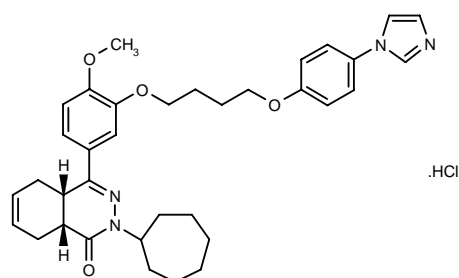
SOURCE – SSP.

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1. Shioiri, N. et al. (SSP Co., Ltd.) *Imidazole deriv. and medicine comprising the same as active ingredient*. CA 2255337, EP 924202.

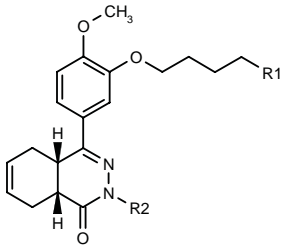
278037

cis-2-Cycloheptyl-4-[3-[4-[4-(1*H*-imidazol-1-yl)phenoxy]butoxy]-4-methoxyphenyl]-1,2,4a,5,8,8a-hexahydrophthalazin-1-one hydrochloride



C₃₅ H₄₂ N₄ O₄ . HCl; Mol wt: 619.2017

ACTION – Bronchodilating agent, a selective inhibitor of phosphodiesterase type 4 (PDE4; $-\log IC_{50} = 9.65$). Other representative compounds within this series of phthalazine derivatives include the following:



Compound	R1	R2	Formula
278038	4-CO2H-PhO	cycloheptyl	C ₃₃ H ₄₀ N ₂ O ₆
278039	4-CONH2-PhOCH2CH2	cycloheptyl	C ₃₅ H ₄₅ N ₃ O ₅
278040	4-Me-2-oxo-2H-benzopyran-7-yl-O	cycloheptyl	C ₃₆ H ₄₂ N ₂ O ₆
278042	4-(CO2HCH2)-2-oxo-2H-1-benzopyran-7-yl-O	Ph	C ₃₆ H ₃₄ N ₂ O ₈

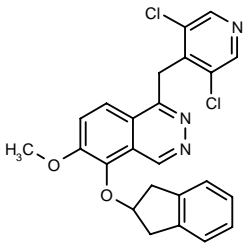
SOURCE – Byk Gulden.

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1. Hatzelmann, A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *New phthalazinones*. WO 9931071.

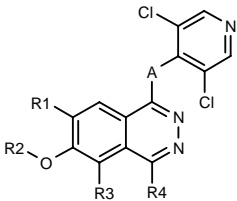
278153

1-(3,5-Dichloropyridin-4-ylmethyl)-5-(indan-2-yloxy)-6-methoxyphthalazine

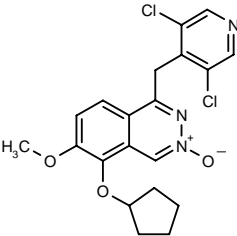


C24 H19 Cl2 N3 O2; Mol wt: 452.3391

ACTION – Phosphodiesterase type 4 (PDE4) and TNF- α inhibitor expected to have potential in the treatment of allergic and inflammatory pathologies including emphysema, chronic bronchitis, asthma and allergic rhinitis. It exhibited nanomolar potency against PDE4 activity and TNF- α production in human monocytes, as well as selectivity relative to PDE3 and PDE5. Other exemplified phthalazine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
278154	H	Me	cyclopentyl-O	H	CH2	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₂
278157	H	CHF2	cyclopentyl-O	H	CH2	C ₂₀ H ₁₇ Cl ₂ F ₂ N ₃ O ₂
278158	H	Me	cyclopentyl-O	H	NH	C ₁₉ H ₁₈ Cl ₂ N ₄ O ₂
278159	H	Me	O(CH2)5Ph	H	CH2	C ₂₆ H ₂₅ Cl ₂ N ₃ O ₂
278161	cyclopentyl-O	Me	H	Et	CH2	C ₂₂ H ₂₃ Cl ₂ N ₃ O ₂



278156: C20 H19 Cl2 N3 O3

SOURCE – Zambon.

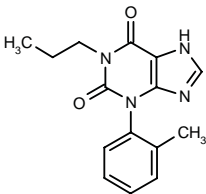
REFERENCES

1. Napoletano, M. et al. (Zambon Group SpA) *Phthalazine derivs. phosphodiesterase 4 inhibitors*. WO 9932456.

278162

3-(2-Methylphenyl)-1-propyl-3,7-dihydro-1H-purine-2,6-dione

3-(2-Methylphenyl)-1-propylxanthine



C15 H16 N4 O2; Mol wt: 284.3174

ACTION – Inhibitor of phosphodiesterase type 4 (PDE4) activity and TNF production with potential in the treatment of asthma, allergy, inflammation and other disorders associated with abnormal production of TNF or PDE4 activity. A representative compound from a series of xanthine derivatives.

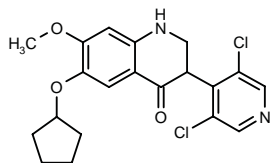
SOURCE – Darwin Discovery.

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1. Dyke, H.J. and Montana, J.G. (Darwin Discovery Ltd.) *Xanthines and their therapeutic use*. US 5919789.

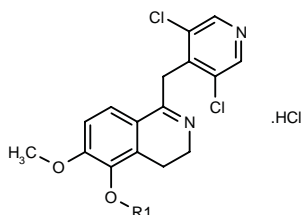
278342

6-(Cyclopentyloxy)-3-(3,5-dichloropyridin-4-yl)-7-methoxy-1,2,3,4-tetrahydroquinolin-4-one



C₂₀ H₂₀ Cl₂ N₂ O₃; Mol wt: 407.2950

ACTION – Phosphodiesterase type 4 (PDE4) and TNF- α inhibitor expected to be useful in the treatment of allergic and inflammatory pathologies, for example, emphysema, chronic bronchitis, asthma and allergic rhinitis. It had IC₅₀ values for PDE4 from human polymorphonuclear leukocytes and TNF- α from human monocytes of 101 and 78.7 nM, respectively, whereas little inhibition of PDE3 and PDE5 was observed. Other representative compounds from this series of benzazine derivatives are:



Compound	R1	Formula
278343	cyclopentyl	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂ ·HCl
278344	(CH ₂) ₅ Ph	C ₂₇ H ₂₈ Cl ₂ N ₂ O ₂ ·HCl

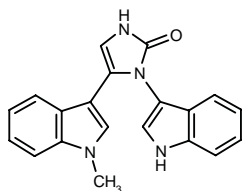
SOURCE – Zambon.

REFERENCES

1. Napoletano, M. et al. (Zambon Group SpA) *Benzazine derivs. phosphodiesterase 4 inhibitors*. WO 9932449.

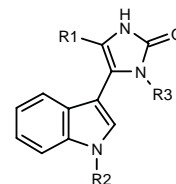
278447

1-(1*H*-Indol-3-yl)-5-(1-methyl-1*H*-indol-3-yl)-2,3-dihydro-1*H*-imidazol-2-one

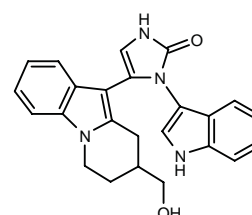


C₂₀ H₁₆ N₄ O; Mol wt: 328.3734

ACTION – Protein kinase C (PKC) inhibitor suitable for oral or inhalation administration and with potential in the treatment of inflammatory airways disorders, e.g., asthma and bronchitis, atopic diseases, e.g., rhinitis and atopic dermatitis, inflammatory bowel diseases, e.g., Crohn's disease and colitis, autoimmune diseases, e.g., multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus and rheumatoid arthritis, malignant diseases, e.g., skin or lung cancer, HIV infection or AIDS and organ transplant rejection. Other specifically claimed 4-indolyl-1,3-dihydroimidazol-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
278448	H	(CH ₂) ₃ NH ₂	3-benzothieryl	C ₂₂ H ₂₀ N ₄ OS
278449	H	3-(NH ₂ CH ₂)- -PhCH ₂	3-indolyl	C ₂₇ H ₂₃ N ₅ O
278450	H	(CH ₂) ₃ S- C(=NH)NH ₂	3-indolyl	C ₂₃ H ₂₂ N ₆ OS
278451	H	H	3-benzothieryl	C ₁₉ H ₁₉ N ₃ OS
278452	CO ₂ Et	Me	1-Naph	C ₂₅ H ₂₁ N ₃ O ₃
278453	H	(CH ₂) ₃ N(Me) ₂	3-indolyl	C ₂₇ H ₂₉ N ₅ O ₃
278455	CH ₂ CONHMe	(CH ₂) ₃ NH ₂	3-indolyl	C ₂₆ H ₂₆ N ₆ O ₂



278454: C₂₄ H₂₂ N₄ O₂

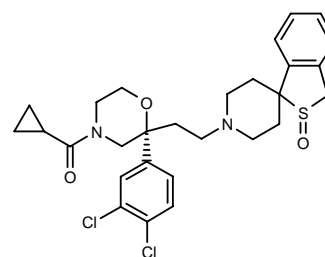
SOURCE – AstraZeneca.

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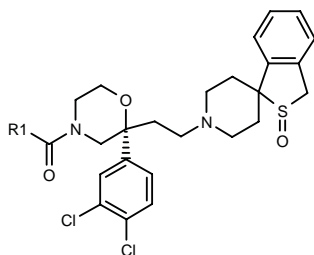
278480

1'-[2-[4-(Cyclopropylcarbonyl)-2(*R*)-(3,4-dichlorophenyl)-morpholin-2-yl]ethyl]spiro[benzo[*c*]thiophen-1(3*H*),4'-piperidine] *S*-oxide



C₂₈ H₃₂ Cl₂ N₂ O₃ S; Mol wt: 547.5438

ACTION – Selective neurokinin NK₂ receptor antagonist, as determined in binding assays by IC₅₀ values of 1000 ng/ml or greater for NK₁ receptors and 0.76 ng/ml for NK₂ receptors. Other representative alicyclic acylated heterocyclic compounds are:



Compound	R1	Formula
278481	cyclobutyl	C ₂₉ H ₃₄ Cl ₂ N ₂ O ₃ S
278482	cyclopentyl	C ₃₀ H ₃₆ Cl ₂ N ₂ O ₃ S

SOURCE – Sankyo.

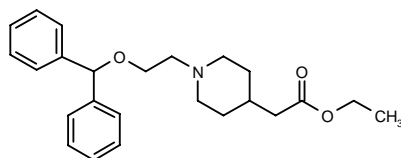
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1. Nishi, T. and Yamaguchi, T. (Sankyo Co., Ltd.) *Alicyclic acylated heterocyclic derivs.* WO 9928307.

BM-113*1-5

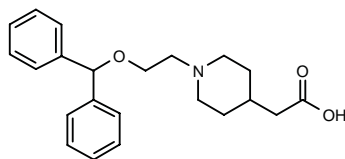
144684

1-[2-(Benzhydryloxy)ethyl]-4-piperidineacetic acid ethyl ester



C₂₄ H₃₁ N O₃; Mol wt: 381.5200

ACTION – Antiallergic agent with antihistaminic and bronchodilating properties. Its major metabolite is:



BM-212 [144686],1-3:** C₂₂ H₂₇ N O₃

SOURCE – Meram.

REFERENCES

1. Buzas, A. et al. (Laboratoires Meram SA) *Benzhydryloxyethylpiperidine derivs., process for their preparation and pharmaceutical compsns., in which they are present* EP 259227, US 4983614.

2. Buzas, A. and Merour, J.Y.F. *Synthesis and antihistaminic activity of new benzhydryloxyethylpiperidines*. 10th Int Symp Med Chem (Aug 15-19, Budapest) 1988, Poster P-128.

3. Duchêne, P. et al. *Pharmacokinetics, metabolism and bioavailability of the new anti-allergic drug BM 113. Part I: Pharmacokinetics and tissular distribution in Sprague-Dawley rats*. *Arzneim-Forsch Drug Res* 1999, 49(6): 504.

4. Duchêne, P. et al. *Pharmacokinetics, metabolism and bioavailability of the new anti-allergic drug BM 113. Part II: Pharmacokinetics in primates after repeated oral or single intravenous administration*. *Arzneim-Forsch Drug Res* 1999, 49(7): 608.

5. Duchêne, P. et al. *Pharmacokinetics, metabolism and bioavailability of the new anti-allergic drug BM 113. Part III: Pharmacokinetics, metabolism, dose dependancy and gender effect after single or repeated administration to human healthy volunteers*. *Arzneim-Forsch Drug Res* 1999, 49(8): 699.

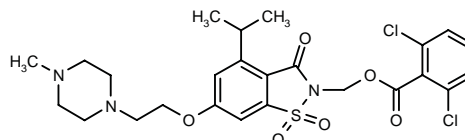
*Identified compound **144684** Drug Data Report 1988, 010(10): 0801.

Identified compound **144686 (see **144684**) Drug Data Report 1988, 010(10): 0801.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

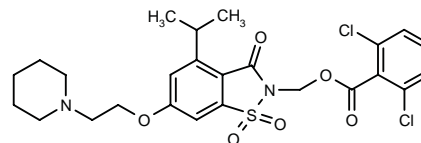
277724

2,6-Dichlorobenzoic acid 4-isopropyl-6-[2-(4-methyl-1-piperazinyl)ethoxy]-1,1,3-trioxo-1,3-dihydro-2H-1,2-benzisothiazol-2-ylmethyl ester



C₂₅ H₂₉ Cl₂ N₃ O₆ S; Mol wt: 570.4911

ACTION – Human leukocyte elastase inhibitor proven active *in vivo* in an acute lung hemorrhage model in hamsters. Potentially useful for the treatment of emphysema, acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease and neutrophil-related lung inflammation. Another related compound is:



277725: C₂₅ H₂₈ Cl₂ N₂ O₆ S

SOURCE – Chinoin.

REFERENCES

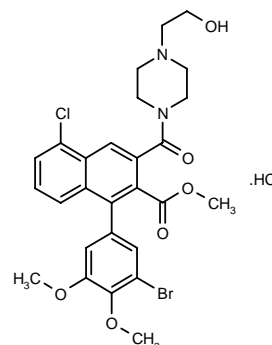
1. Varga, M. et al. *In vivo active saccharine type inhibitors of human leukocyte elastase*. *Fundam Clin Pharmacol* 1999, 13(Suppl. 1): Abst PS203.

CARDIOVASCULAR DRUGS

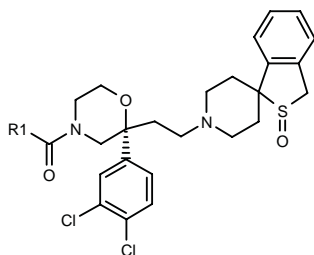
ANTIHYPERTENSIVE DRUGS

263038

1-(3-Bromo-4,5-dimethoxyphenyl)-5-chloro-3-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]naphthalene-2-carboxylic acid methyl ester hydrochloride



C₂₇ H₂₈ Br Cl N₂ O₆ . HCl; Mol wt: 628.3441



Compound	R1	Formula
278481	cyclobutyl	C ₂₉ H ₃₄ Cl ₂ N ₂ O ₃ S
278482	cyclopentyl	C ₃₀ H ₃₆ Cl ₂ N ₂ O ₃ S

SOURCE – Sankyo.

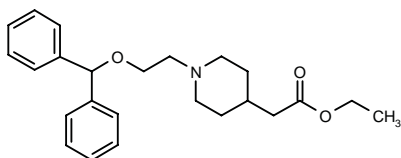
REFERENCES

1. Nishi, T. and Yamaguchi, T. (Sankyo Co., Ltd.) *Alicyclic acylated heterocyclic derivs.* WO 9928307.

BM-113*1-5

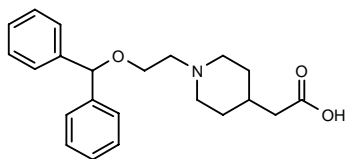
144684

1-[2-(Benzhydryloxy)ethyl]-4-piperidineacetic acid ethyl ester



C₂₄ H₃₁ N O₃; Mol wt: 381.5200

ACTION – Antiallergic agent with antihistaminic and bronchodilating properties. Its major metabolite is:



BM-212 [144686],1-3:** C₂₂ H₂₇ N O₃

SOURCE – Meram.

REFERENCES

1. Buzas, A. et al. (Laboratoires Meram SA) *Benzhydryloxyethylpiperidine derivs., process for their preparation and pharmaceutical compsns., in which they are present* EP 259227, US 4983614.

2. Buzas, A. and Merour, J.Y.F. *Synthesis and antihistaminic activity of new benzhydryloxyethylpiperidines*. 10th Int Symp Med Chem (Aug 15-19, Budapest) 1988, Poster P-128.

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4. Duchêne, P. et al. *Pharmacokinetics, metabolism and bioavailability of the new anti-allergic drug BM 113. Part II: Pharmacokinetics in primates after repeated oral or single intravenous administration*. *Arzneim-Forsch Drug Res* 1999, 49(7): 608.

5. Duchêne, P. et al. *Pharmacokinetics, metabolism and bioavailability of the new anti-allergic drug BM 113. Part III: Pharmacokinetics, metabolism, dose dependancy and gender effect after single or repeated administration to human healthy volunteers*. *Arzneim-Forsch Drug Res* 1999, 49(8): 699.

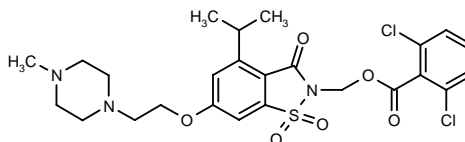
*Identified compound **144684** Drug Data Report 1988, 010(10): 0801.

Identified compound **144686 (see **144684**) Drug Data Report 1988, 010(10): 0801.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

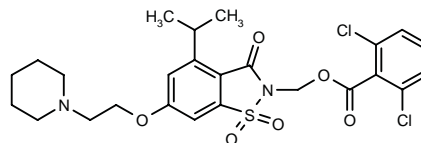
277724

2,6-Dichlorobenzoic acid 4-isopropyl-6-[2-(4-methyl-1-piperazinyl)ethoxy]-1,1,3-trioxo-1,3-dihydro-2H-1,2-benzisothiazol-2-ylmethyl ester



C₂₅ H₂₉ Cl₂ N₃ O₆ S; Mol wt: 570.4911

ACTION – Human leukocyte elastase inhibitor proven active *in vivo* in an acute lung hemorrhage model in hamsters. Potentially useful for the treatment of emphysema, acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease and neutrophil-related lung inflammation. Another related compound is:



277725: C₂₅ H₂₈ Cl₂ N₂ O₆ S

SOURCE – Chinoin.

REFERENCES

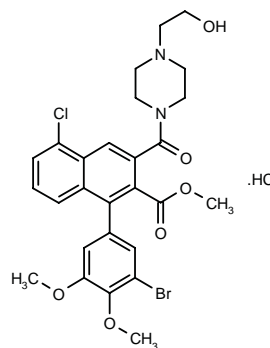
1. Varga, M. et al. *In vivo active saccharine type inhibitors of human leukocyte elastase*. *Fundam Clin Pharmacol* 1999, 13(Suppl. 1): Abst PS203.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

263038

1-(3-Bromo-4,5-dimethoxyphenyl)-5-chloro-3-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]naphthalene-2-carboxylic acid methyl ester hydrochloride



C₂₇ H₂₈ Br Cl N₂ O₆ . HCl; Mol wt: 628.3441

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor (IC_{50} = 6.2 nM) with > 16,000-fold selectivity over other PDE isoforms (PDE1, PDE2, PDE3, PDE4); it showed relaxant activity on rat aorta (EC_{50} = 0.10 μ M). Potentially useful for the treatment of cardiovascular diseases such as hypertension, angina, congestive heart failure and impotence.

SOURCE – Tanabe.

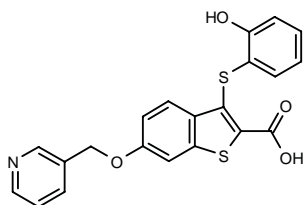
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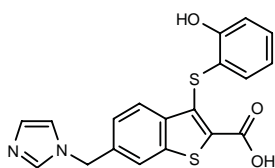
277425

3-(2-Hydroxyphenylsulfanyl)-6-(pyridin-3-ylmethoxy)-1-benzothiophene-2-carboxylic acid



C21 H15 N O4 S2; Mol wt: 409.4845

ACTION – Endothelin receptor antagonist with selectivity for ET_A receptors, giving a pA_2 of 7.83 for inhibition of $ET-1$ -induced contractions in rat aorta. Potentially useful in the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, male erectile dysfunction, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischemia or cyclosporin-induced nephrotoxicity. Another exemplified benzothiophene derivative is:



277426: C19 H14 N2 O3 S2

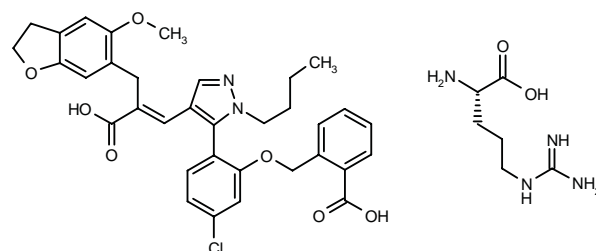
SOURCE – Pfizer.

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1. Dack, K.N. and Dickinson, R.P. (Pfizer Ltd.;Pfizer Inc.) *Benzothiophene derivs. useful in therapy*. CA 2255165, EP 921124.

277807

2-[2-[1-Butyl-4-[2-carboxy-3-(5-methoxy-2,3-dihydro-1-benzofuran-6-yl)-1(*E*)-propenyl]-1*H*-pyrazol-5-yl]-5-chlorophenoxymethyl]benzoic acid monoarginine salt



C34 H33 Cl N2 O7 . C6 H14 N4 O2; Mol wt: 791.2973

ACTION – New salt of a known endothelin receptor antagonist that has been found to have higher bioavailability as compared to the disodium salt (SB-247083⁺) or dissolution-enhancing formulations of the diacid. As found in studies in dogs, the mean oral bioavailability of the monoarginine salt in capsules was 13.8%, which was comparable to that of the disodium salt given intraduodenally in a nonaqueous solution and superior to that of various formulations of the diacid and capsule formulations of the disodium salt. Potentially useful in the treatment of hypertension, chronic renal failure, cerebrovascular diseases, benign prostatic hypertrophy, congestive heart failure, unstable angina, pulmonary hypertension, atherosclerosis and stroke or subarachnoid hemorrhage.

SOURCE – SmithKline Beecham.

REFERENCES

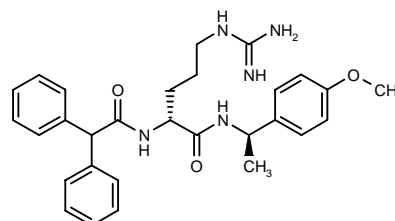
1. Flisak, J.R. et al. (SmithKline Beecham Corp.) *(E)-3-[1-N-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid monoargininyl salt*. WO 9929685.

*Drug Data Report 1998, 020(07): 0582.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

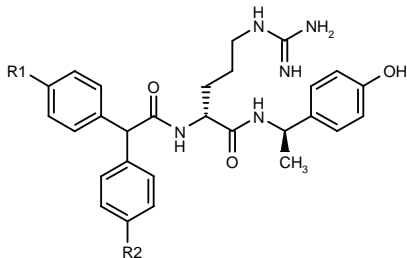
275665

N^{α} -(2,2-Diphenylacetyl)- N^1 -[1(*R*)-(4-methoxyphenyl)-ethyl]-D-argininamide



C29 H35 N5 O3; Mol wt: 501.6275

ACTION – Selective neuropeptide Y (NPY) Y₁ receptor antagonist with potential in the treatment of cardiovascular diseases and vasoconstriction, i.e., migraine, Horton’s syndrome, Raynaud’s disease, vasospasm after subarachnoid hemorrhage, angina pectoris, coronary infarction, heart failure, cardiac arrhythmias, hypertension, septic shock and stroke. Other specifically claimed compounds from this series of D-arginamide derivatives include the following:



Compound	R1	R2	Formula
275666	H	H	C ₂₈ H ₃₃ N ₅ O ₃
275667	H	Cl	C ₂₈ H ₃₂ ClN ₅ O ₃
275668	Cl	Cl	C ₂₈ H ₃₁ Cl ₂ N ₅ O ₃
275669	H	OH	C ₂₈ H ₃₃ N ₅ O ₄

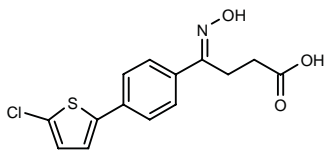
SOURCE – AstraZeneca.

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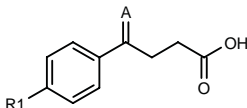
275859

4-[4-(5-Chlorothien-2-yl)phenyl]-4-(hydroxyimino)butyric acid



C14 H12 Cl N O3 S; Mol wt: 309.7718

ACTION – Inhibitor of matrix metalloproteinases (MMPs), particularly gelatinase A (MMP-2; IC₅₀ = 0.014 μM), stromelysin 1 (MMP-3; IC₅₀ = 0.105 μM) and collagenase 3 (MMP-13; IC₅₀ = 0.12 μM). Claimed for use in the treatment of atherosclerosis, heart failure, restenosis, aortic aneurysm, periodontal disease, burns, wounds, corneal ulceration, cancer, arthritis, osteoporosis, multiple sclerosis, inflammation, pain and neurodegenerative disorders. Within this series of heteroaryl butyric acid derivatives, the following are also included:



Compound	R1	A	Formula
275860	1-pyrazolyl	-N(OH)-	C ₁₃ H ₁₃ N ₃ O ₃
275861	5-Cl-2-thienyl	-O-	C ₁₄ H ₁₁ ClO ₃ S

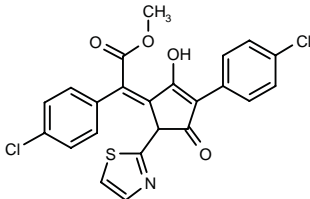
SOURCE – Warner-Lambert.

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277374

2-(4-Chlorophenyl)-2-[3-(4-chlorophenyl)-2-hydroxy-4-oxo-5-(2-thiazolyl)-2-cyclopenten-1-ylidene]acetic acid methyl ester



C23 H15 Cl2 N O4 S; Mol wt: 472.3465

ACTION – Nonpeptide macrophage class A scavenger receptor (SR-A) antagonist proven to inhibit the uptake of a modified LDL (Dil-AcLDL) in transfected HEK-293 cells (IC₅₀ = 13 μM), as well as in human peripheral and rat peritoneal macrophages (IC₅₀ = 21 and 17 μM, respectively). Compound was able to inhibit both the degradation and binding/uptake of [¹²⁵I]-AcLDL in HEK-293 cells (K_i = 18 and 40 μM, respectively). Potentially useful for preventing plaque formation in patients with ischemic heart disease, stroke and atherosclerosis.

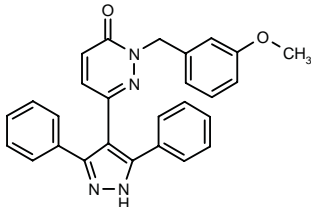
SOURCE – SmithKline Beecham.

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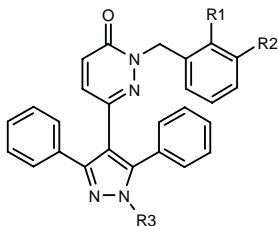
277812

6-(3,5-Diphenyl-1H-pyrazol-4-yl)-2-(3-methoxybenzyl)-pyridazin-3(2H)-one

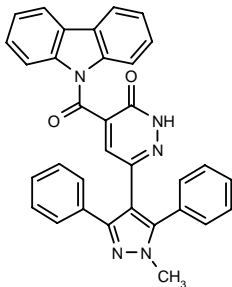


C27 H22 N4 O2; Mol wt: 434.4968

ACTION – Potent dual adenosine A₁ and A₂ receptor antagonist potentially useful for the treatment or prevention of ischemic heart diseases such as angina pectoris, peripheral vascular diseases such as intermittent claudication, cerebral ischemia, migraine, diabetes, depression, Parkinson’s disease, etc. Other exemplified compounds from this series of pyrazoles include the following:



Compound	R1	R2	R3	Formula
277813	Me	H	H	C ₂₇ H ₂₂ N ₄ O
277814	H	OMe	4-MeO-PhCH ₂	C ₃₅ H ₃₀ N ₄ O ₃
277815	H	OMe	Me	C ₂₈ H ₂₄ N ₄ O ₂



277884: C33 H23 N5 O2

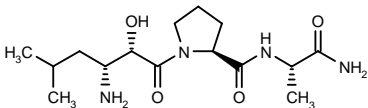
SOURCE – Fujisawa.

REFERENCES

1. Akahane, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Pyrazole cpds. and medicinal use thereof*. WO 9924424.

277842

N-[3(R)-Amino-2(S)-hydroxy-5-methylhexanoyl]-L-prolyl-L-alaninamide



C15 H28 N4 O4; Mol wt: 328.4102

ACTION – Potent inhibitor of aminopeptidase P with some selectivity for human membrane-bound enzyme (IC₅₀ = 0.23 μM) over the two cytosolic isoforms of the enzyme derived from heart and platelets (IC₅₀ = 6.3 and 1.2 μM, respectively); compound also inhibited monkey and rat membrane-bound aminopeptidase P (IC₅₀ = 0.13 and 0.56 μM, respectively), but was less effective against bovine enzyme (IC₅₀ = 4.5 μM), prolidase (IC₅₀ = 2.2 μM) and leucyl aminopeptidase (IC₅₀ = 12 μM). Potential lead compound for the development of more potent compounds with potential for the treatment of cardiovascular disorders via potentiation of endogenous bradykinin.

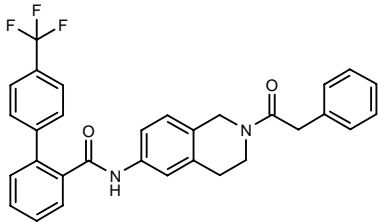
SOURCE – Pharmacia & Upjohn.

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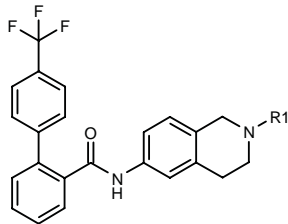
278166

N-[2-(2-Phenylacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-4'-(trifluoromethyl)biphenyl-2-carboxamide



C31 H25 F3 N2 O2; Mol wt: 514.5445

ACTION – Antiatherosclerotic and hypolipidemic agent that reduces serum cholesterol and triglyceride levels by virtue of its ability to inhibit microsomal triglyceride transfer protein (MTP) and apolipoprotein B (ApoB) secretion. Within this series of specifically claimed N-(1,2,3,4-tetrahydroisoquinolin-6-yl)biphenyl-2-carboxamide derivatives, the following are also included:



Compound	R1	Formula
278167	CONHPh	C ₃₀ H ₂₄ F ₃ N ₃ O ₂
278168	i-PrSO ₂	C ₂₆ H ₂₅ F ₃ N ₂ O ₃ S
278169	cyclopropyl-NHCS	C ₂₇ H ₂₃ F ₃ N ₂ O ₂ S
278170	2,6,6-(Me)3-2-cyclohexenyl-CH ₂	C ₃₃ H ₃₅ F ₃ N ₂ O
278171	t-BuOCO	C ₂₈ H ₂₇ F ₃ N ₂ O ₃
278172	2-thienyl-CH ₂ CO	C ₂₉ H ₂₃ F ₃ N ₂ O ₂ S
278173	H	C ₂₃ H ₁₉ F ₃ N ₂ O
278174	4-(CH ₂ OH)-3-(CH ₂ CH ₂ OH)-Ph	C ₃₂ H ₂₉ F ₃ N ₂ O ₃

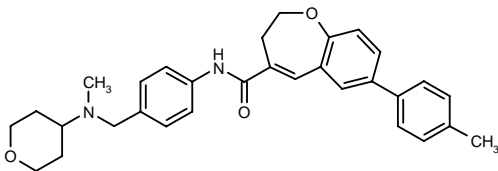
SOURCE – Pfizer.

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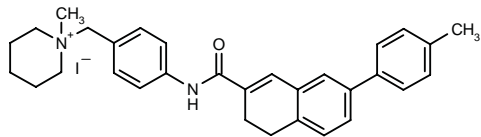
278345

7-(4-Methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepin-4-carboxamide



C31 H34 N2 O3; Mol wt: 482.6206

ACTION – MCP-1 (monocyte chemoattractant protein-1) receptor antagonist proven to inhibit [¹²⁵I]-recombinant human MCP-1 binding by 80% at a concentration of 1 μM, and MCP-1-induced chemotaxis by 89%. Potentially useful in the treatment of a wide range of disorders, particularly myocardial infarction, myocarditis, cardiomyopathy, chronic heart failure, restenosis following angioplasty, inflammatory disorders such as rheumatoid arthritis and arteriosclerosis, organ transplant rejection, diabetes and complications thereof, tumors and infectious diseases. Another representative compound from this series of anilide derivatives is:



278346: C31 H35 I N2 O

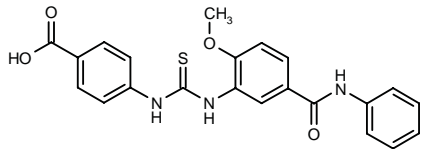
SOURCE – Takeda.

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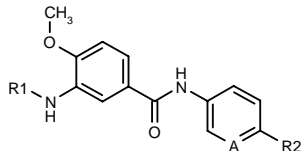
278393

4-[3-[2-Methoxy-5-(*N*-phenylcarbamoyl)phenyl]-thioureido]benzoic acid



C22 H19 N3 O4 S; Mol wt: 421.4751

ACTION – 15-Lipoxygenase and monocyte chemotaxis inhibitor expected to be useful in the treatment or prevention of inflammatory disorders and atherosclerosis. It inhibited rabbit reticulocyte 15-LO with an IC₅₀ of 104 nM. In rabbits with hypercholesterolemia-induced atherosclerosis, this compound (10 mg/kg mixed with the diet) reduced the extent of aortic arch lesions by 49%, aortic cholesteryl ester content by 28% and aortic arch cross-sectional lesion area by 90% compared to controls. Other exemplified thiourea and benzamide compounds are:



Compound	R1	R2	A	Formula
278394	3,5-(Cl)2-Ph	H	CH	C ₂₀ H ₁₆ Cl ₂ N ₂ O ₂
278395	3-NO2-PhNHCS	H	CH	C ₂₁ H ₁₈ N ₄ O ₄ S
278396	3,5-(Cl)2-PhNHCS	H	CH	C ₂₁ H ₁₇ Cl ₂ N ₃ O ₂ S
278397	3,5-(Cl)2-PhNHCS	F	CH	C ₂₁ H ₁₆ Cl ₂ FN ₃ O ₂ S
278398	3,4-(Cl)2-NHCS	H	N	C ₂₀ H ₁₆ Cl ₂ N ₄ O ₂ S
278399	SO2C12H25	H	CH	C ₂₆ H ₃₈ N ₂ O ₄ S
278400	SO2C8H17	H	CH	C ₂₂ H ₃₀ N ₂ O ₄ S
278401	SO2C10H21	H	CH	C ₂₄ H ₃₄ N ₂ O ₄ S

SOURCE – Warner-Lambert.

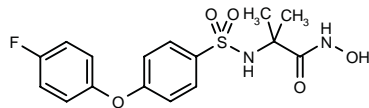
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CP-471474

273490

2-[4-(4-Fluorophenoxy)phenylsulfonamido]-*N*-hydroxy-2-methylpropionamide



C16 H17 F N2 O5 S; Mol wt: 368.3833

ACTION – Broad-spectrum matrix metalloproteinase (MMP) inhibitor with high selectivity for MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-9 (gelatinase B) and MMP-13 (collagenase 3), giving IC₅₀ values of 0.7, 16, 13 and 0.9 nM, respectively, versus 1170 nM for MMP-1 (interstitial collagenase). Compound showed a good pharmacokinetic profile, with high absolute oral bio-availability in mice (80.3%). In a model of experimental myocardial infarction in mice, compound (120 mg/kg p.o. twice a day for 4 days) attenuated left ventricular dilatation, producing a significantly smaller increase in end-systolic and end-diastolic dimensions and areas at both midpapillary and apical levels compared with placebo-treated infarcted mice.

SOURCE – Pfizer.

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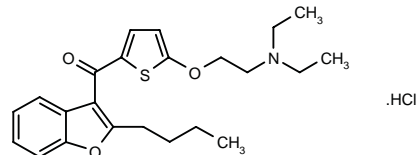
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ANTIARRHYTHMIC DRUGS

E047/1

209716

1-(2-Butyl-1-benzofuran-3-yl)-1-[5-[2-(diethylamino)-ethoxy]-2-thienyl]methanone hydrochloride



C23 H29 N O3 S . HCl; Mol wt: 436.0130

ACTION – Rapid-acting antiarrhythmic agent, an amiodarone derivative able to block both the rapid and slow component of the delayed rectifier potassium current, as well as sodium currents and, to a lesser extent, calcium currents. Compound causes a uniform prolongation of conduction intervals and cardiac refractoriness. In conscious chronically instrumented dogs, it suppressed postmyocardial infarct arrhythmias and was much more effective than bretylium, amiodarone, flecainide and lidocaine in reducing the number of premature ventricular contractions and the rate and duration of tachycardic runs. In a dose-finding phase II study in 40 patients undergoing coronary bypass surgery, compound reduced the incidence of postoperative ventricular arrhythmias by almost 100%, with no effects on hemodynamic parameters and no negative inotropic and negative chronotropic effects.

SOURCE – Ebewe.

REFERENCES

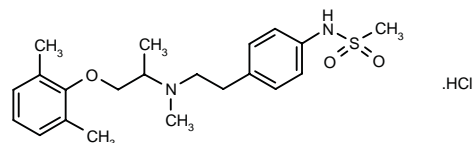
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MONOGRAPH – Mayrleitner, M. *E047/1.* Drugs Fut 1999, 24(9): in press.

GYKI-16638

263649

N-[4-[2-[*N*-[2-(2,6-Dimethylphenoxy)-1-methylethyl]-*N*-methylamino]ethyl]phenyl]methanesulfonamide hydrochloride



C21 H30 N2 O3 S . HCl; Mol wt: 427.0059

ACTION – Antiarrhythmic agent with both class Ib and class III effects; it exerts strong antiarrhythmic activity in various animal models, without significant cardiac and extracardiac side effects. Compound (5 µM) decreased the maximal rate of depolarization (35%) and lengthened the action potential duration (22%) in dog right ventricular papillary muscle, and it completely blocked the rapid component of the delayed rectifier potassium current in single dog ventricular myocytes. In anesthetized rabbits, compound (0.03 mg/kg) was able to protect against reperfusion-induced arrhythmias and ventricular fibrillation and it increased survival.

SOURCES – Albert Szent-Györgyi Medical University, Szeged (HU); Institute for Drug Research, Budapest (HU).

REFERENCES

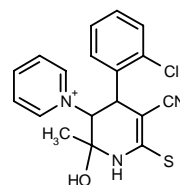
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HEART FAILURE THERAPY

IOS-7319

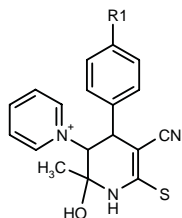
277765

4'-(2-Chlorophenyl)-5'-cyano-2'-hydroxy-2'-methyl-6'-sulfanyl-1',2',3',4'-tetrahydro-1,3'-bipyridinium inner salt



C18 H16 Cl N3 O S; Mol wt: 357.8634

ACTION – Cardiotonic agent, a sulfur analogue of milrinone with improved inotropic activity in spontaneously beating rat atria (84% increase in force of contraction vs. 65% for milrinone at 10 µM) and reduced general toxicity (LD₅₀ > 2000 mg/kg i.p. vs. 55-117 mg/kg i.p. for milrinone). Other related compounds are:



Compound	R1	Formula
IOS-7566 [277766]	NO2	C ₁₈ H ₁₆ N ₄ O ₃ S
IOS-7565 [277767]	OH	C ₁₈ H ₁₇ N ₃ O ₂ S
IOS-7318 [277768]	H	C ₁₈ H ₁₇ N ₃ OS

SOURCE – Latvian Institute of Organic Synthesis, Riga (LV).

REFERENCES

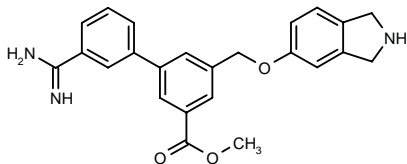
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

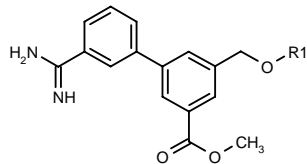
277693

3'-Amidino-5-(2,3-dihydro-1*H*-isoindol-5-yloxymethyl)-biphenyl-3-carboxylic acid methyl ester



C24 H23 N3 O3; Mol wt: 401.4637

ACTION – Factor Xa inhibitor with an IC₅₀ value against human factor Xa of 0.1-1 µM and good selectivity relative to thrombin; it doubled the activated partial thromboplastin time in human plasma at concentrations of 1-10 µM. Other exemplified biphenylamidine derivatives are:



Compound	R1	Formula
277695	2-[MeC(=NH)]-2,3-dihydro-5-isoindolyl	C ₂₆ H ₂₆ N ₄ O ₃
277697	3-(NH2CH2CH2)-Ph	C ₂₄ H ₂₅ N ₃ O ₃

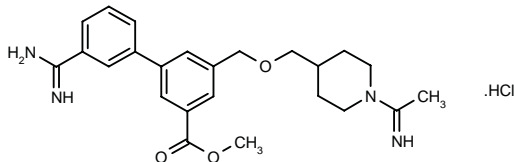
SOURCE – Teijin.

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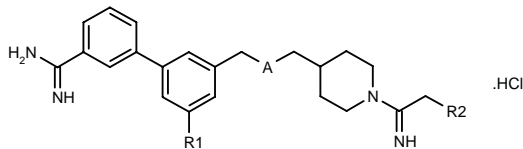
277705

3'-Amidino-5-[1-(ethanimidoyl)piperidin-4-ylmethoxy-methyl]biphenyl-3-carboxylic acid methyl ester hydrochloride



C24 H30 N4 O3 . HCl; Mol wt: 458.9869

ACTION – Anticoagulant and antithrombotic agent, a selective human factor Xa inhibitor (IC₅₀ = 0.063 µM) with no effect on thrombin (IC₅₀ > 1000 µM). Compound was shown to double the activated partial thromboplastin time (aPTT) in human plasma at a concentration of 0.76 µM. Bioavailability was 10% following oral administration of 10 mg/kg to mice. Other compounds from this series of biphenylamidine derivatives include the following:



Compound	R1	R2	A	Formula
277706	CO2H	H	NH	C ₂₃ H ₂₉ N ₅ O ₂ .HCl
277707	CH2CH2CO2H	H	O	C ₂₅ H ₃₂ N ₄ O ₃ .HCl
277708	CO2H	OH	NH	C ₂₃ H ₂₉ N ₅ O ₃ .HCl

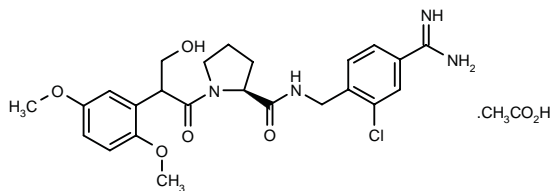
SOURCE – Teijin.

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277728

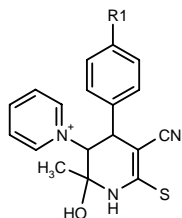
N-(4-Amidino-2-chlorobenzyl)-1-[2-(2,5-dimethoxy-phenyl)-3-hydroxypropionyl]-L-prolinamide acetate



C24 H29 Cl N4 O5 . C2 H4 O2; Mol wt: 549.0207

ACTION – Anticoagulant and antithrombotic agent, a competitive inhibitor of trypsin-like serine proteases, especially thrombin, proven to double the thrombin clotting time (TT) of human plasma at a concentration < 0.3 µM. Another exemplified compound is:

ACTION – Cardiotonic agent, a sulfur analogue of milrinone with improved inotropic activity in spontaneously beating rat atria (84% increase in force of contraction vs. 65% for milrinone at 10 µM) and reduced general toxicity (LD₅₀ > 2000 mg/kg i.p. vs. 55-117 mg/kg i.p. for milrinone). Other related compounds are:



Compound	R1	Formula
IOS-7566 [277766]	NO2	C ₁₈ H ₁₆ N ₄ O ₃ S
IOS-7565 [277767]	OH	C ₁₈ H ₁₇ N ₃ O ₂ S
IOS-7318 [277768]	H	C ₁₈ H ₁₇ N ₃ OS

SOURCE – Latvian Institute of Organic Synthesis, Riga (LV).

REFERENCES

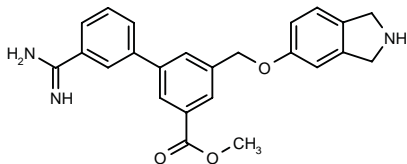
1. Krauze, A. et al. Search for agents possessing inotropic activity in a series of sulfur analogues of cardiotonic drug milrinone. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PM128.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

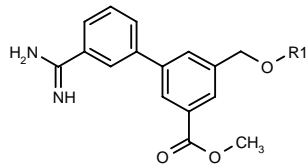
277693

3'-Amidino-5-(2,3-dihydro-1*H*-isoindol-5-yloxymethyl)-biphenyl-3-carboxylic acid methyl ester



C24 H23 N3 O3; Mol wt: 401.4637

ACTION – Factor Xa inhibitor with an IC₅₀ value against human factor Xa of 0.1-1 µM and good selectivity relative to thrombin; it doubled the activated partial thromboplastin time in human plasma at concentrations of 1-10 µM. Other exemplified biphenylamidine derivatives are:



Compound	R1	Formula
277695	2-[MeC(=NH)]-2,3-dihydro-5-isoindolyl	C ₂₆ H ₂₆ N ₄ O ₃
277697	3-(NH2CH2CH2)-Ph	C ₂₄ H ₂₅ N ₃ O ₃

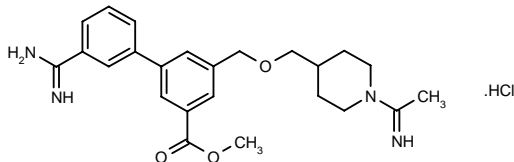
SOURCE – Teijin.

REFERENCES

1. Takano, Y. et al. (Teijin Ltd.) Biphenylamidine derivs. WO 9926919.

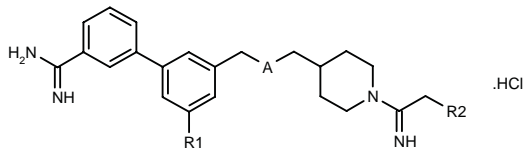
277705

3'-Amidino-5-[1-(ethanimidoyl)piperidin-4-ylmethoxy-methyl]biphenyl-3-carboxylic acid methyl ester hydrochloride



C24 H30 N4 O3 . HCl; Mol wt: 458.9869

ACTION – Anticoagulant and antithrombotic agent, a selective human factor Xa inhibitor (IC₅₀ = 0.063 µM) with no effect on thrombin (IC₅₀ > 1000 µM). Compound was shown to double the activated partial thromboplastin time (aPTT) in human plasma at a concentration of 0.76 µM. Bioavailability was 10% following oral administration of 10 mg/kg to mice. Other compounds from this series of biphenylamidine derivatives include the following:



Compound	R1	R2	A	Formula
277706	CO2H	H	NH	C ₂₃ H ₂₉ N ₅ O ₂ .HCl
277707	CH2CH2CO2H	H	O	C ₂₅ H ₃₂ N ₄ O ₃ .HCl
277708	CO2H	OH	NH	C ₂₃ H ₂₉ N ₅ O ₃ .HCl

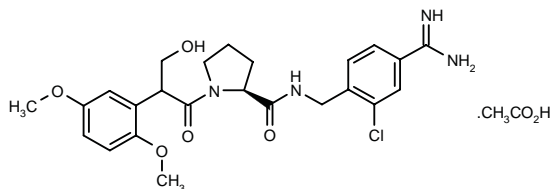
SOURCE – Teijin.

REFERENCES

1. Hara, T. et al. (Teijin Ltd.) Biphenylamidine derivs. WO 9926918.

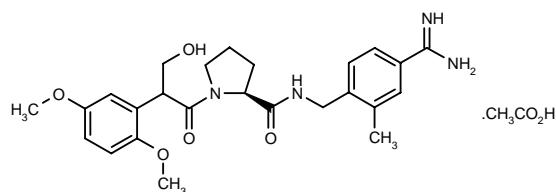
277728

N-(4-Amidino-2-chlorobenzyl)-1-[2-(2,5-dimethoxy-phenyl)-3-hydroxypropionyl]-L-prolinamide acetate



C24 H29 Cl N4 O5 . C2 H4 O2; Mol wt: 549.0207

ACTION – Anticoagulant and antithrombotic agent, a competitive inhibitor of trypsin-like serine proteases, especially thrombin, proven to double the thrombin clotting time (TT) of human plasma at a concentration < 0.3 µM. Another exemplified compound is:



277729: C₂₅ H₃₂ N₄ O₅ · C₂ H₄ O₂

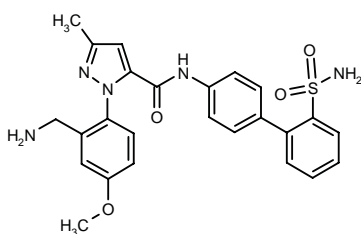
SOURCE – AstraZeneca.

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1. Karlsson, O. et al. (Astra AB) *New cpds.* WO 9929664.

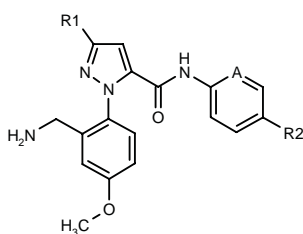
278228

1-[2-(Aminomethyl)-4-methoxyphenyl]-N-[2'-(aminosulfonyl)biphenyl-4-yl]-3-methyl-1*H*-pyrazole-5-carboxamide



C₂₅ H₂₅ N₅ O₄ S; Mol wt: 491.5695

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, especially human factor Xa. Other specifically claimed compounds from this series of 5-membered nitrogen-containing heteroaryl derivatives include the following:



Compound	R1	R2	A	Formula
278229	CF ₃	2-(MeSO ₂)-Ph	CH	C ₂₆ H ₂₃ F ₃ N ₄ O ₄ S
278230	Et	1-pyrrolidinyl-CO	CH	C ₂₅ H ₂₉ N ₅ O ₃
278231	CF ₃	2-(MeSO ₂)-Ph	N	C ₂₅ H ₂₂ F ₃ N ₅ O ₄ S
278232	Et	5-Me-1-imidazolyl	CH	C ₂₄ H ₂₆ N ₆ O ₂

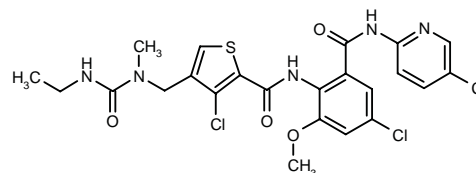
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Galemno, R.A. Jr. et al. (DuPont Pharmaceuticals Co.) *Nitrogen containing hetero-aromatics with ortho-substd. P1's as factor Xa inhibitors.* WO 9932454.

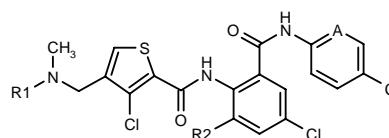
278378

5-Chloro-2-[3-chloro-4-(3-ethyl-1-methylureidomethyl)-thiophen-2-ylcarboxamido]-N-(5-chloro-2-pyridinyl)-3-methoxybenzamide

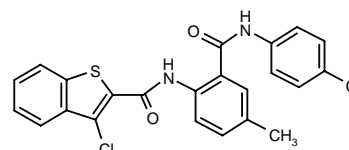


C₂₃ H₂₂ Cl₃ N₅ O₄ S; Mol wt: 570.8828

ACTION – Anticoagulant, a factor Xa inhibitor potentially useful for the prophylaxis of long-term risk following myocardial infarction, as well as the prophylaxis of deep vein thrombosis following orthopedic surgery or the prophylaxis of selected patients following a transient ischemic attack. Other exemplified ortho-anthranilamide derivatives include the following:



Compound	R1	R2	A	Formula
278380	1-pyrrolidinyl-CH ₂ CH ₂	OCH ₂ CH ₂ OAc	N	C ₂₉ H ₃₂ Cl ₃ N ₅ O ₅ S
278383	2-oxazolyl	4-morpholinyl	CH	C ₂₇ H ₂₈ Cl ₃ N ₅ O ₄ S



278379: C₂₃ H₁₆ Cl₂ N₂ O₂ S

SOURCE – Schering AG.

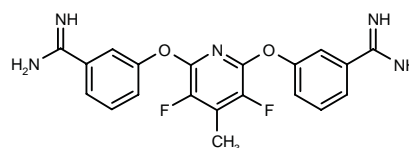
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1. Arnaiz, D.O. et al. (Schering AG) *Ortho-anthranilamide derivs. as anticoagulants.* WO 9932477.

ZK-805623

266729

3,3'-[(3,5-Difluoro-4-methyl-2,6-pyridinediyl)bis(oxy)]-benzenecarboximidamide



C₂₀ H₁₇ F₂ N₅ O₂; Mol wt: 397.3833

ACTION – Antithrombotic agent, a potent and selective human factor Xa inhibitor (K_i = 13 nM) with high selectivity over human thrombin and bovine trypsin (K_i = 22,000 and 810 nM, respectively).

SOURCE – Berlex.

REFERENCES

1. Buckman, B.O. et al. (Berlex Laboratories, Inc.) *Benzamidine derivs. their preparation and their use as anti-coagulants*. EP 813525, US 5691364, WO 9628427.

2. Phillips, G. et al. *Design, synthesis, and activity of 2,6-diphenoxypyridine-derived factor Xa inhibitors*. J Med Chem 1999, 42(10): 1749.

3. Phillips, G.B. et al. *Discovery of N-[2-[5-[amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-N-methylglycine (ZK-807834): A potent, selective, and orally active inhibitor of the blood coagulation enzyme factor Xa*. J Med Chem 1998, 41(19): 3557.

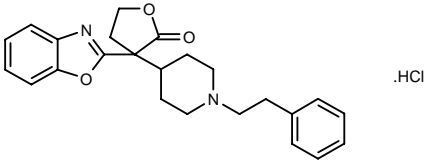
4. Phillips, G.B. et al. *Design, synthesis and biological activity of novel factor Xa inhibitors. 2. 2,6-Diphenoxypyridine inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 122.

5. Whitlow, M. et al. *Structural studies of factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 133.

ANTIPLATELET THERAPY

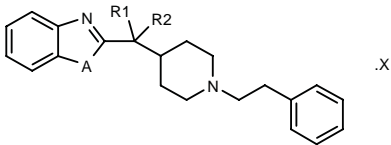
276282

3-(Benzoxazol-2-yl)-3-[1-(2-phenylethyl)piperidin-4-yl]tetrahydrofuran-2-one hydrochloride

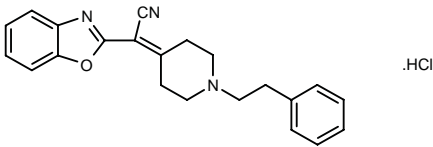


C24 H26 N2 O3 . HCl; Mol wt: 426.9413

ACTION – 5-HT₂ receptor antagonist and platelet aggregation inhibitor proven to inhibit 5-HT-induced contractions of rat arterial preparations (IC₅₀ < 0.5 μM) and collagen-induced rabbit platelet aggregation (IC₅₀ < 1.0 μM). *In vivo* studies demonstrated its ability to inhibit 5-HTP-induced head twitches in mice with ID₅₀ values of < 1000 μg/kg i.v. and to inhibit carrageenan-induced peripheral infarction with ID₅₀ values of 10 mg/kg p.o. or less. Other exemplified piperidine derivatives are:



Compound	R1	R2	A	X	Formula
276284	CN	H	O	HCl	C ₂₂ H ₂₃ N ₃ O.HCl
276285	CN	Et	O	HCl	C ₂₄ H ₂₇ N ₃ O.HCl
276286	(CH ₂) ₂ OAc	CN	O		C ₂₆ H ₂₉ N ₃ O ₃
276287	CH ₂ CH ₂ OMe	CN	O		C ₂₅ H ₂₉ N ₃ O ₂
276288	2-THP-OCH ₂ CH ₂	CN	O		C ₂₈ H ₃₅ N ₃ O ₃
276289	CH ₂ CH ₂ OH	CN	O		C ₂₄ H ₂₇ N ₃ O ₂
276290	-CH ₂ CH ₂ OC(=NH)-		O		C ₂₄ H ₂₇ N ₃ O ₂
276291	-CH ₂ CH ₂ OC(=NH)-		S		C ₂₄ H ₂₇ N ₃ OS



276283: C22 H21 N3 O . HCl

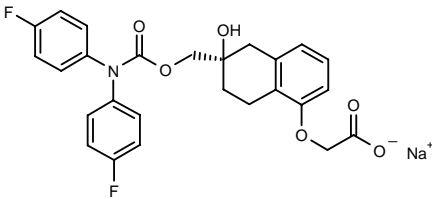
SOURCE – Toa Eiyo.

REFERENCES

1. Goto, T. et al. (Toa Eiyo Ltd.) *Novel piperidine derivs., their preparation method and agents for circulatory organ, containing the same*. JP 99080155.

278305

2-[6(R)-[N,N-Bis(4-fluorophenyl)carbamoyloxymethyl]-6-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yloxy]acetic acid sodium salt



C26 H22 F2 N Na O6; Mol wt: 505.4468

ACTION – Platelet aggregation inhibitor proven to act as a PGI₂ (IP) receptor agonist. It inhibited ADP-induced human platelet aggregation by over 85% at a concentration of 0.1 μM. Potentially useful in the treatment or prevention of arterial obstruction, restenosis or ischemic complications following coronary angioplasty, arteriosclerosis, cerebrovascular diseases, ischemic heart disease and dermatosis.

SOURCE – Fujisawa.

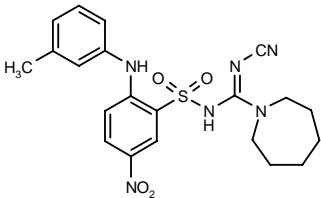
REFERENCES

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BM-519

277837

N²-Cyano-N¹-[2-(3-methylphenylamino)-5-nitrophenyl-sulfonyl]azepine-1-carboxamide



C21 H24 N6 O4 S; Mol wt: 456.5246

ACTION – Potent and selective TxA_2 antagonist, a molecule combining the pharmacophores of BM-144 and BM-500 with nanomolar affinity for human platelet TxA_2 (TP) receptors ($\text{IC}_{50} = 22 \text{ nM}$) comparable to the prostanoid SQ-29548 ($\text{IC}_{50} = 22 \text{ nM}$). Compound prevented platelet aggregation induced by arachidonic acid or the TxA_2 agonist U-46619 ($\text{IC}_{50} = 0.36$ and $0.48 \mu\text{M}$, respectively) and it relaxed aortic rings precontracted with U-46619 ($\text{IC}_{50} = 1.2 \text{ nM}$), whereas it had no effect on contractions induced by 30 mM KCl or other prostaglandins. It was also devoid of the diuretic activity of the parent molecule torasemide. Potentially useful for the treatment of cardiovascular and pulmonary disorders characterized by vasoconstriction, bronchoconstriction or platelet aggregation.

SOURCE – University of Namur, Namur (BE).

REFERENCES

1. Masereel, B. et al. *BM-519, a novel non-carboxylic thromboxane A_2 antagonist*. *Fundam Clin Pharmacol* 1999, 13(Suppl. 1): Abst PM14.

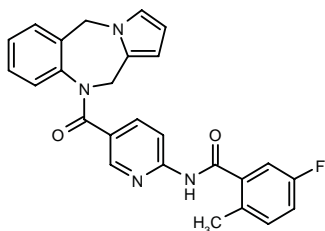
RENAL-UROLOGIC DRUGS

DIURETICS

CL-385004*

241430

N-[5-(10,11-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl)pyridin-2-yl]-5-fluoro-2-methylbenzamide



C26 H21 F N4 O2; Mol wt: 440.4810

ACTION – Arginine vasopressin (AVP) receptor antagonist with nanomolar binding affinity for V_{1a} and V_2 receptors ($\text{IC}_{50} = 33$ and 4 nM , respectively). *In vivo*, compound (10 mg/kg/day in the diet for 2 months) antagonized the antidiuretic and pressor effects of AVP, increasing the urine flow rate, decreasing urine osmolality and attenuating the decrease in cardiac output. Potentially useful for the treatment of fluid retention in congestive heart failure, liver cirrhosis, nephrotic syndrome, CNS injuries, lung diseases and hyponatremia.

SOURCE – American Home Products.

REFERENCES

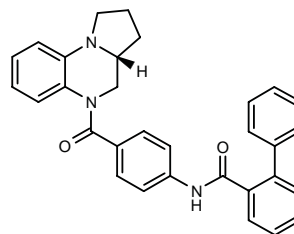
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2. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5700796, WO 9749708.
3. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5753648, WO 9749707.
4. Aranapakam, V. et al. *5-Fluoro-2-methyl-N-[5-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-yl carbonyl]-2-pyridinyl]benzamide (CL-385004) and analogs as orally active arginine vasopressin receptor antagonists*. *Bioorg Med Chem Lett* 1999, 9(13): 1737.
5. Hartupsee, D.A. et al. *Effects of CL-385004, a nonpeptidic vasopressin V_{1A}/V_2 receptor antagonist, in rat model of heart failure*. *Circulation* 1997, 96(8, Suppl.): Abst 3416.

*Identified compound **241430** (see **239891**) Drug Data Report 1996, 018(10): 0886.

VP-365

278141

N-[4-[1,2,3,3a(*R*),4,5-Hexahydropyrrolo[1,2-*a*]quinoxalin-5-ylcarbonyl]phenyl]biphenyl-2-carboxamide



C31 H27 N3 O2; Mol wt: 473.5733

ACTION – Arginine vasopressin (AVP) receptor antagonist with high affinity for V_2 and high selectivity relative to V_{1a} receptors ($\text{IC}_{50} = 1.18$ and 127 nM , respectively). Compound showed diuretic activity in rats with an ED_{300} (oral dose required to triple urine volume compared to control rats) of 0.31 mg/kg . Potentially useful as a diuretic agent in conditions such as heart failure, hypertension, hyponatremia and dysfunction in the secretion of anti-diuretic hormones.

SOURCE – Wakamoto.

REFERENCES

1. Ohtake, Y. et al. (Wakamoto Pharmaceutical Co., Ltd.) *Biphenyl derivs. and medicinal compns*. WO 9843976.
2. Ohtake, Y. et al. *Novel vasopressin V_2 receptor-selective antagonists, pyrrolo[2,1-*a*]quinoxaline and pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives*. *Bioorg Med Chem* 1999, 7(6): 1247.

ACTION – Potent and selective TxA_2 antagonist, a molecule combining the pharmacophores of BM-144 and BM-500 with nanomolar affinity for human platelet TxA_2 (TP) receptors ($\text{IC}_{50} = 22 \text{ nM}$) comparable to the prostanoid SQ-29548 ($\text{IC}_{50} = 22 \text{ nM}$). Compound prevented platelet aggregation induced by arachidonic acid or the TxA_2 agonist U-46619 ($\text{IC}_{50} = 0.36$ and $0.48 \mu\text{M}$, respectively) and it relaxed aortic rings precontracted with U-46619 ($\text{IC}_{50} = 1.2 \text{ nM}$), whereas it had no effect on contractions induced by 30 mM KCl or other prostaglandins. It was also devoid of the diuretic activity of the parent molecule torasemide. Potentially useful for the treatment of cardiovascular and pulmonary disorders characterized by vasoconstriction, bronchoconstriction or platelet aggregation.

SOURCE – University of Namur, Namur (BE).

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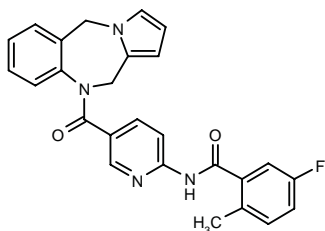
RENAL-UROLOGIC DRUGS

DIURETICS

CL-385004*

241430

N-[5-(10,11-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl)pyridin-2-yl]-5-fluoro-2-methylbenzamide



C26 H21 F N4 O2; Mol wt: 440.4810

ACTION – Arginine vasopressin (AVP) receptor antagonist with nanomolar binding affinity for V_{1a} and V_2 receptors ($\text{IC}_{50} = 33$ and 4 nM , respectively). *In vivo*, compound (10 mg/kg/day in the diet for 2 months) antagonized the antidiuretic and pressor effects of AVP, increasing the urine flow rate, decreasing urine osmolality and attenuating the decrease in cardiac output. Potentially useful for the treatment of fluid retention in congestive heart failure, liver cirrhosis, nephrotic syndrome, CNS injuries, lung diseases and hyponatremia.

SOURCE – American Home Products.

REFERENCES

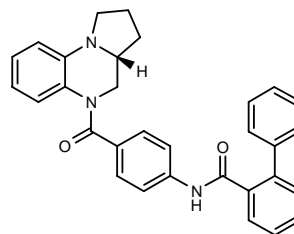
1. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. JP 99500106, US 5536718, WO 9622293.
2. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5700796, WO 9749708.
3. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5753648, WO 9749707.
4. Aranapakam, V. et al. *5-Fluoro-2-methyl-N-[5-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-yl carbonyl]-2-pyridinyl]benzamide (CL-385004) and analogs as orally active arginine vasopressin receptor antagonists*. *Bioorg Med Chem Lett* 1999, 9(13): 1737.
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*Identified compound **241430** (see **239891**) Drug Data Report 1996, 018(10): 0886.

VP-365

278141

N-[4-[1,2,3,3a(*R*),4,5-Hexahydropyrrolo[1,2-*a*]quinoxalin-5-ylcarbonyl]phenyl]biphenyl-2-carboxamide



C31 H27 N3 O2; Mol wt: 473.5733

ACTION – Arginine vasopressin (AVP) receptor antagonist with high affinity for V_2 and high selectivity relative to V_{1a} receptors ($\text{IC}_{50} = 1.18$ and 127 nM , respectively). Compound showed diuretic activity in rats with an ED_{300} (oral dose required to triple urine volume compared to control rats) of 0.31 mg/kg . Potentially useful as a diuretic agent in conditions such as heart failure, hypertension, hyponatremia and dysfunction in the secretion of anti-diuretic hormones.

SOURCE – Wakamoto.

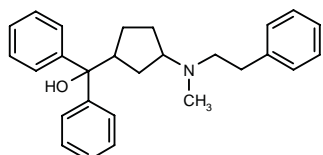
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2. Ohtake, Y. et al. *Novel vasopressin V_2 receptor-selective antagonists, pyrrolo[2,1-*a*]quinoxaline and pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives*. *Bioorg Med Chem* 1999, 7(6): 1247.

TREATMENT OF URINARY INCONTINENCE

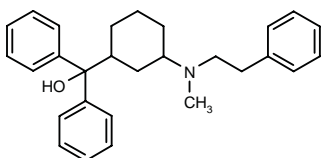
275472

1-[3-[*N*-Methyl-*N*-(2-phenylethyl)amino]cyclopentyl]-1,1-diphenylmethanol



C₂₇ H₃₁ N O; Mol wt: 385.5479

ACTION – Muscarinic M₃ receptor antagonist with selectivity for bladder M₃ receptors over trachea M₃ receptors as well as M₂ receptors, as demonstrated by pA₂ values of 8.1, 7.6 and 7.1 when tested *in vitro* for its ability to inhibit carbachol-induced contractions in guinea pig bladder, trachea and left atrium preparations, respectively. Potentially useful in the treatment of urinary incontinence, respiratory disorders such as asthma, gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease, and nausea and vomiting. Another exemplified compound from this series of aminocycloalkylmethanol derivatives is:



275474: C₂₈ H₃₃ N O

SOURCE – Tokyo Tanabe.

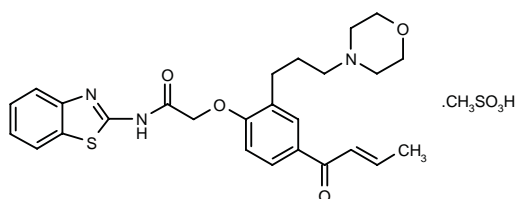
REFERENCES

1. Ohno, N. et al. (Tokyo Tanabe Co., Ltd.) *Aminocycloalkyl-methanol cpds.* JP 99071331.

TREATMENT OF RENAL DISEASES

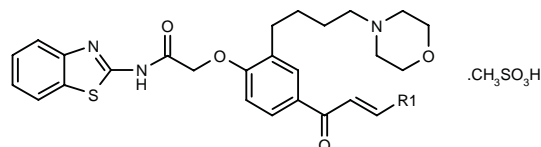
277588

N-(2-Benzothiazolyl)-2-[4-[2(*E*)-butenoyl]-2-[3-(4-morpholinyl)propyl]phenoxy]acetamide methanesulfonate



C₂₆ H₂₉ N₃ O₄ S . C H₄ O₃ S; Mol wt: 575.7037

ACTION – Protein kinase C (PKC) inhibitor (IC₅₀ = 0.07 μM using enzyme purified from rat brain) proven active in a model of renal failure induced by ischemia–reperfusion in rats, significantly decreasing blood urea nitrogen and serum creatinine levels at 3 mg/kg p.o. Other exemplified compounds from this series of benzothiazole derivatives are:



Compound	R1	Formula
277589	Me	C ₂₇ H ₃₁ N ₃ O ₄ S.CH ₄ O ₃ S
277591	3-THP	C ₃₁ H ₃₇ N ₃ O ₅ S.CH ₄ O ₃ S

SOURCE – Otsuka.

REFERENCES

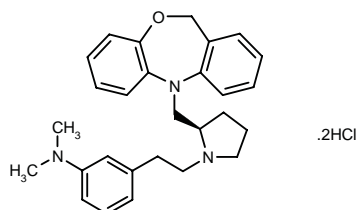
1. Mori, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzothiazole derivs.* JP 99130761.

GASTROINTESTINAL DRUGS

IRRITABLE BOWEL SYNDROME THERAPY

275892

3-[2-[2(*R*)-(5,11-Dihydrodibenzo[*b,e*][1,4]oxazepin-5-ylmethyl)pyrrolidin-1-yl]ethyl]-*N,N*-dimethylaniline dihydrochloride



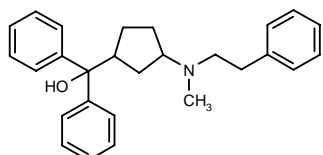
C₂₈ H₃₃ N₃ O . 2HCl; Mol wt: 500.5105

ACTION – Agent for the treatment of gastrointestinal disorders, particularly irritable bowel syndrome, with potent calcium channel antagonist-activity, as demonstrated by IC₅₀ values of 57 and 17 nM, respectively, against K⁺-induced contractions in rat aorta and ileum preparations. Compound is reported to possess good water solubility. Other compounds from this series of 5,11-dihydrodibenzo[*b,e*][1,4]oxazepine derivatives include the following:

TREATMENT OF URINARY INCONTINENCE

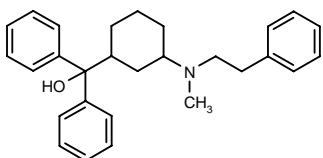
275472

1-[3-[*N*-Methyl-*N*-(2-phenylethyl)amino]cyclopentyl]-1,1-diphenylmethanol



C₂₇ H₃₁ N O; Mol wt: 385.5479

ACTION – Muscarinic M₃ receptor antagonist with selectivity for bladder M₃ receptors over trachea M₃ receptors as well as M₂ receptors, as demonstrated by pA₂ values of 8.1, 7.6 and 7.1 when tested *in vitro* for its ability to inhibit carbachol-induced contractions in guinea pig bladder, trachea and left atrium preparations, respectively. Potentially useful in the treatment of urinary incontinence, respiratory disorders such as asthma, gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease, and nausea and vomiting. Another exemplified compound from this series of aminocycloalkylmethanol derivatives is:



275474: C₂₈ H₃₃ N O

SOURCE – Tokyo Tanabe.

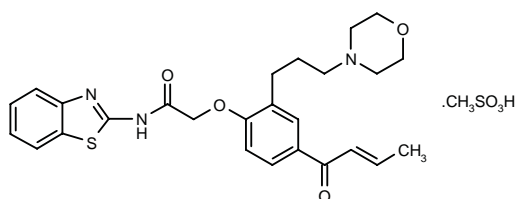
REFERENCES

1. Ohno, N. et al. (Tokyo Tanabe Co., Ltd.) *Aminocycloalkyl-methanol cpds.* JP 99071331.

TREATMENT OF RENAL DISEASES

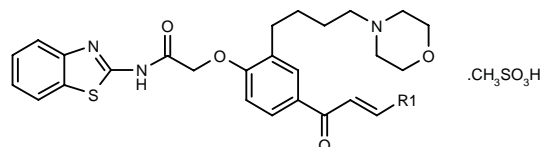
277588

N-(2-Benzothiazolyl)-2-[4-[2(*E*)-butenoyl]-2-[3-(4-morpholinyl)propyl]phenoxy]acetamide methanesulfonate



C₂₆ H₂₉ N₃ O₄ S · C H₄ O₃ S; Mol wt: 575.7037

ACTION – Protein kinase C (PKC) inhibitor (IC₅₀ = 0.07 μM using enzyme purified from rat brain) proven active in a model of renal failure induced by ischemia–reperfusion in rats, significantly decreasing blood urea nitrogen and serum creatinine levels at 3 mg/kg p.o. Other exemplified compounds from this series of benzothiazole derivatives are:



Compound	R1	Formula
277589	Me	C ₂₇ H ₃₁ N ₃ O ₄ S·CH ₄ O ₃ S
277591	3-THP	C ₃₁ H ₃₇ N ₃ O ₅ S·CH ₄ O ₃ S

SOURCE – Otsuka.

REFERENCES

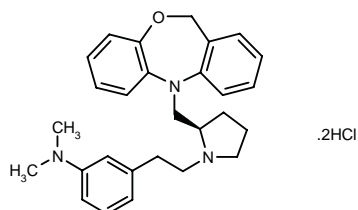
1. Mori, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzothiazole derivs.* JP 99130761.

GASTROINTESTINAL DRUGS

IRRITABLE BOWEL SYNDROME THERAPY

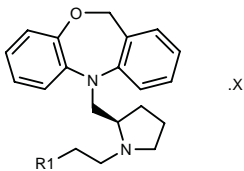
275892

3-[2-[2(*R*)-(5,11-Dihydrodibenzo[*b,e*][1,4]oxazepin-5-ylmethyl)pyrrolidin-1-yl]ethyl]-*N,N*-dimethylaniline dihydrochloride



C₂₈ H₃₃ N₃ O · 2HCl; Mol wt: 500.5105

ACTION – Agent for the treatment of gastrointestinal disorders, particularly irritable bowel syndrome, with potent calcium channel antagonist-activity, as demonstrated by IC₅₀ values of 57 and 17 nM, respectively, against K⁺-induced contractions in rat aorta and ileum preparations. Compound is reported to possess good water solubility. Other compounds from this series of 5,11-dihydrodibenzo[*b,e*][1,4]oxazepine derivatives include the following:



Compound	R1	X	Formula
275893	4-N(Me)2-Ph	2HCl	C ₂₈ H ₃₃ N ₃ O.2HCl
275894	4-N(Et)2-Ph	2HCl	C ₃₀ H ₃₇ N ₃ O.2HCl
275895	3-MeNH-Ph	2HCl	C ₂₇ H ₃₁ N ₃ O.2HCl
275896	4-MeO-PhCH2	HCl	C ₂₆ H ₃₂ N ₂ O ₂ .HCl
275897	3-N(Me)2-PhCH2	2HCl	C ₂₉ H ₃₅ N ₃ O.2HCl

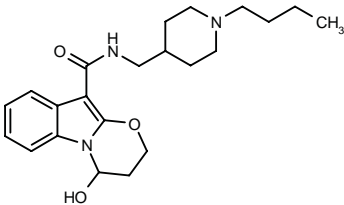
SOURCE – Ajinomoto.

REFERENCES

1. Sakata, K. et al. (Ajinomoto Co., Inc.) 5,11-Dihydrodibenz[b,e]oxazepine derivs. and medicinal compsn. containing the same. WO 9912925.

277649

(±)-N-(1-Butyl-4-piperidinylmethyl)-4-hydroxy-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide



C22 H31 N3 O3; Mol wt: 385.5049

ACTION – Metabolite of piboserod*, a known 5-HT₄ receptor antagonist, with potent and selective activity at 5-HT₄ receptors in functional assays using guinea pig longitudinal muscle-myenteric plexus preparations. Potentially useful for treating irritable bowel syndrome, gastroesophageal reflux disease, dyspepsia, atrial arrhythmias, stroke, anxiety and migraine.

SOURCE – SmithKline Beecham.

REFERENCES

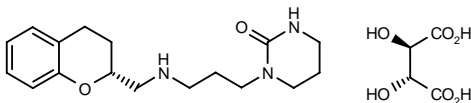
1. Hossner, F. et al. (SmithKline Beecham plc) *Pharmaceuticals*. WO 9929697.

*See **SB-207266A** Drug Data Rep 1996, 018(03): 0249.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

277810

1-[3-[3,4-Dihydro-2H-1-benzopyran-2(R)-ylmethyl-amino]propyl]hexahydropyrimidin-2-one L-(+)-tartrate



C17 H25 N3 O2 . C4 H6 O6; Mol wt: 453.4889

ACTION – Fundic relaxant, as demonstrated in conscious dogs when given at 0.63 mg/kg s.c, with little or no vasoconstrictor activity (EC₅₀ > 1 μM in pig basilar artery). Potentially useful in the treatment of conditions related to impaired fundic relaxation such as dyspepsia, early satiety, bloating and anorexia; compound is also believed to be of use in the treatment of irritable bowel syndrome. A specifically claimed compound from a series of benzodioxan, benzofuran and benzopyran derivatives.

SOURCE – Janssen.

REFERENCES

1. Wigerinck, P.T.B.P. et al. (Janssen Pharmaceutica NV) (Benzodioxan, benzofuran or benzopyran) derivs. having fundic relaxation properties. WO 9929687.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

ZSIG45

277514

Human thyroid protein

ACTION – Novel human protein strongly expressed in thyroid and pituitary gland, with potential in the treatment of thyroid disorders, ischemia–reperfusion injury and inflammatory disorders, as well as for use in diagnostic methods. Also disclosed are genes encoding this protein and antibodies to the protein.

SOURCE – ZymoGenetics.

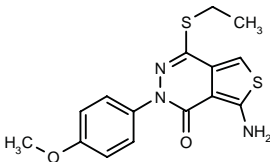
REFERENCES

1. Sheppard, P.O. and Deisher, T.A. (ZymoGenetics, Inc.) *Human thyroid protein zsig45 and DNA encoding same*. WO 9928467.

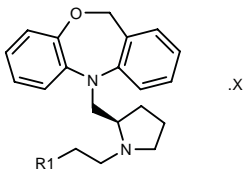
ANTIDIABETIC DRUGS

275706

7-Amino-4-(ethylsulfanyl)-2-(4-methoxyphenyl)thieno[3,4-d]pyridazin-1(2H)-one



C15 H15 N3 O2 S2; Mol wt: 333.4345



Compound	R1	X	Formula
275893	4-N(Me)2-Ph	2HCl	C ₂₈ H ₃₃ N ₃ O.2HCl
275894	4-N(Et)2-Ph	2HCl	C ₃₀ H ₃₇ N ₃ O.2HCl
275895	3-MeNH-Ph	2HCl	C ₂₇ H ₃₁ N ₃ O.2HCl
275896	4-MeO-PhCH2	HCl	C ₂₆ H ₃₂ N ₂ O ₂ .HCl
275897	3-N(Me)2-PhCH2	2HCl	C ₂₉ H ₃₅ N ₃ O.2HCl

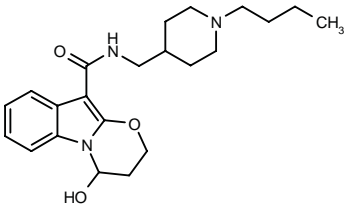
SOURCE – Ajinomoto.

REFERENCES

1. Sakata, K. et al. (Ajinomoto Co., Inc.) 5,11-Dihydrodibenz[b,e]oxazepine derivs. and medicinal compsn. containing the same. WO 9912925.

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(±)-N-(1-Butyl-4-piperidinylmethyl)-4-hydroxy-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide



C22 H31 N3 O3; Mol wt: 385.5049

ACTION – Metabolite of piboserod*, a known 5-HT₄ receptor antagonist, with potent and selective activity at 5-HT₄ receptors in functional assays using guinea pig longitudinal muscle-myenteric plexus preparations. Potentially useful for treating irritable bowel syndrome, gastroesophageal reflux disease, dyspepsia, atrial arrhythmias, stroke, anxiety and migraine.

SOURCE – SmithKline Beecham.

REFERENCES

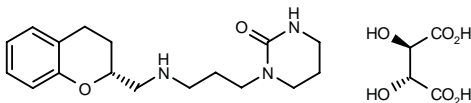
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*See **SB-207266A** Drug Data Rep 1996, 018(03): 0249.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

277810

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ACTION – Fundic relaxant, as demonstrated in conscious dogs when given at 0.63 mg/kg s.c, with little or no vasoconstrictor activity (EC₅₀ > 1 μM in pig basilar artery). Potentially useful in the treatment of conditions related to impaired fundic relaxation such as dyspepsia, early satiety, bloating and anorexia; compound is also believed to be of use in the treatment of irritable bowel syndrome. A specifically claimed compound from a series of benzodioxan, benzofuran and benzopyran derivatives.

SOURCE – Janssen.

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1. Wigerinck, P.T.B.P. et al. (Janssen Pharmaceutica NV) (Benzodioxan, benzofuran or benzopyran) derivs. having fundic relaxation properties. WO 9929687.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

ZSIG45

277514

Human thyroid protein

ACTION – Novel human protein strongly expressed in thyroid and pituitary gland, with potential in the treatment of thyroid disorders, ischemia–reperfusion injury and inflammatory disorders, as well as for use in diagnostic methods. Also disclosed are genes encoding this protein and antibodies to the protein.

SOURCE – ZymoGenetics.

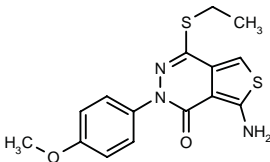
REFERENCES

1. Sheppard, P.O. and Deisher, T.A. (ZymoGenetics, Inc.) *Human thyroid protein zsig45 and DNA encoding same*. WO 9928467.

ANTIDIABETIC DRUGS

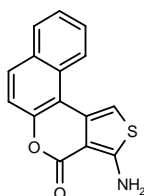
275706

7-Amino-4-(ethylsulfanyl)-2-(4-methoxyphenyl)thieno[3,4-d]pyridazin-1(2H)-one



C15 H15 N3 O2 S2; Mol wt: 333.4345

ACTION – Inhibitor of protein tyrosine phosphatases (PTPases) such as PTP1B ($K_i = 2 \mu\text{M}$), CD45, PTP1C, PTP α , LAR and HePTP with potential in the treatment of type I or II diabetes, impaired glucose tolerance, insulin resistance, obesity, cancer, psoriasis, osteoporosis, autoimmune disorders, AIDS, allergic diseases, coagulation disorders, Alzheimer's disease and infectious diseases. Another exemplified compound is:



275707: C₁₅ H₉ N O₂ S

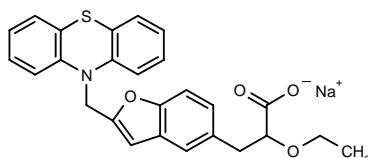
SOURCES – Novo Nordisk; Ontogen.

REFERENCES

1. Andersen, H.S. et al. (Novo Nordisk A/S; Ontogen Corp.) *Modules of protein tyrosine phosphatases (PTPases)*. WO 9915529.

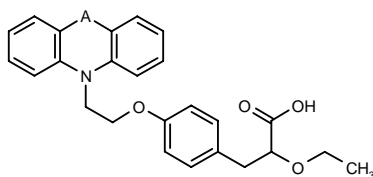
275970

2-Ethoxy-3-[2-(phenothiazin-10-ylmethyl)benzofuran-5-yl]propionic acid sodium salt



C₂₆ H₂₂ N Na O₄ S; Mol wt: 467.5188

ACTION – Hypoglycemic and hypolipidemic agent proven to lower blood glucose and triglyceride levels in *db/db* mice when administered at 3 mg/kg/day p.o. x 6 days (52 and 61% reduction, respectively). Other representative tricyclic compounds include the following:



Compound	A	Formula
275972	S	C ₂₅ H ₂₅ NO ₄ S
275974	O	C ₂₅ H ₂₅ NO ₅

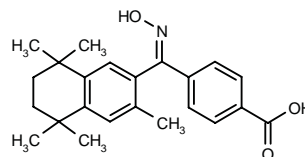
SOURCE – Dr. Reddy's Research Foundation, Hyderabad (IN).

REFERENCES

1. Lohray, B.B. et al. (Dr. Reddy's Research Foundation) *Novel tricyclic cpds. and their use in medicine; process for their preparation and pharmaceutical compsns. containing them*. WO 9919313.

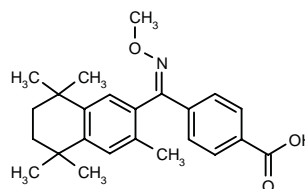
277069

(Z)-4-[(Hydroxyimino)(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]benzoic acid



C₂₃ H₂₇ N O₃; Mol wt: 365.4703

ACTION – Retinoid X receptor (RXR) agonist with high affinity for all three RXR subtypes ($K_i = 6, 5$ and 5 nM , respectively, against [³H]-LGD-1069 binding to RXR α , RXR β and RXR γ subtypes) and high selectivity relative to retinoic acid receptors (RAR α , RAR β and RAR γ ; $K_i > 10,000 \text{ nM}$). Compound specifically activates transcriptional activity of RXR α , RXR β and RXR γ ($\text{EC}_{50} = 7, 14$ and 7 nM , respectively) while showing no effect on the activity of RAR subtypes, and it activates the RXR:PPAR γ heterodimer ($\text{EC}_{50} = 14 \text{ nM}$) and induces the differentiation of 3T3-L1 cells to adipocytes. Potentially useful for the treatment of metabolic disorders such as type II diabetes and obesity. Another related compound is:



277071: C₂₄ H₂₉ N O₃

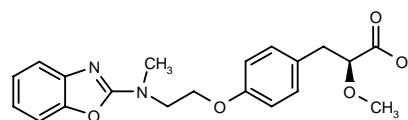
SOURCE – Ligand.

REFERENCES

1. Canan Koch, S.S. et al. *Synthesis of retinoid X receptor-specific ligands that are potent inducers of adipogenesis in 3T3-L1 cells*. J Med Chem 1999, 42(4): 742.

277400

(-)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2(S)-methoxypropionic acid



C₂₀ H₂₂ N₂ O₅; Mol wt: 370.4028

Colorless solid, *m.p.* 116-9 °C, $[\alpha]_D^{25} -10^\circ$ (*c* 0.55, MeOH).

ACTION – Nonthiazolidinedione insulin sensitizer that acts by specifically binding to ($\text{IC}_{50} = 3.9 \text{ nM}$) and activating the peroxisome proliferator-activated receptor PPAR γ ; it enhanced glucose transport *in vitro* in differentiated 3T3-L1 adipocytes ($\text{EC}_{50} = 6.3 \text{ nM}$). *In vivo*, compound showed antihyperglycemic activity in genetically obese mice ($\text{ED}_{25} = 3 \mu\text{mol/kg}$ in the diet). Potentially useful for the treatment of type II diabetes.

SOURCE – SmithKline Beecham.

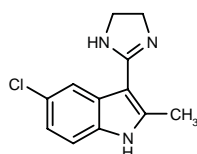
REFERENCES

1. Haigh, D. and Sime, J. (SmithKline Beecham plc) *Heterocyclic cpds. as pharmaceutical*. US 5869495, WO 9401420.

2. Haigh, D. et al. *Non-thiazolidinedione antihyperglycaemic agents. Part 3: The effects of stereochemistry on the potency of α -methoxy- β -phenylpropanoic acids*. Bioorg Med Chem 1999, 7(5): 821.

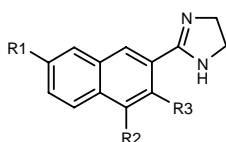
277915

5-Chloro-3-(4,5-dihydro-1H-imidazol-2-yl)-2-methyl-1H-indole

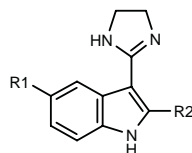


C₁₂H₁₂ClN₃; Mol wt: 233.7008

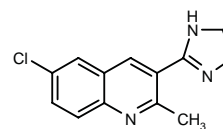
ACTION – Hypoglycemic agent useful in the treatment of diabetes, especially type II diabetes, diabetic complications, metabolic disorders and related diseases characterized by impaired glucose disposal. It potentiates the secretion of insulin from β -cells under conditions of high glucose, with minimal effects under conditions of low glucose. Other specifically claimed imidazoline compounds are:



Compound	R1	R2	R3	Formula
277917	4-Me-Ph	H	OCH ₂ CH ₂ OMe	C ₂₃ H ₂₄ N ₂ O ₂
277921	Ph	H	OCH ₂ CH ₂ OMe	C ₂₂ H ₂₂ N ₂ O ₂
277922	5-Cl-2-thienyl	H	OCH ₂ CH ₂ OEt	C ₂₁ H ₂₁ ClN ₂ O ₂ S
277923	2-F-Ph	H	OCH ₂ CH ₂ OMe	C ₂₂ H ₂₁ FN ₂ O ₂
277924	4-MeO-Ph	H	O(CH ₂) ₃ OMe	C ₂₄ H ₂₆ N ₂ O ₃
277997	H	4-Cl-Ph	OCH ₂ CH ₂ OMe	C ₂₂ H ₂₁ ClN ₂ O ₂
277998	H	2,4-(Cl)2-Ph	OCH ₂ CH ₂ OMe	C ₂₂ H ₂₀ Cl ₂ N ₂ O ₂



Compound	R1	R2	Formula
277918	CF ₃	Me	C ₁₃ H ₁₂ F ₃ N ₃
277919	Cl	3-Cl-Ph	C ₁₇ H ₁₃ Cl ₂ N ₃
277920	Cl	2-Cl-Ph	C ₁₇ H ₁₃ Cl ₂ N ₃



277916: C₁₃H₁₂ClN₃

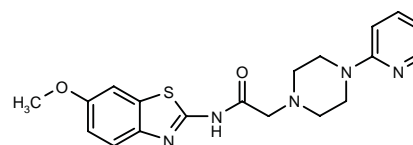
SOURCE – Lilly.

REFERENCES

1. Jirousek, M.R. et al. (Eli Lilly and Company) *Hypoglycemic imidazoline cpds*. EP 924209, WO 9932112, WO 9932482.

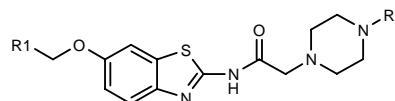
278192

N-(6-Methoxybenzothiazol-2-yl)-2-[4-(pyridin-2-yl)-piperazin-1-yl]acetamide



C₁₉H₂₁N₅O₂S; Mol wt: 383.4739

ACTION – Hypoglycemic agent shown to dose-dependently decrease blood glucose levels in diabetic C57BL/Ks *db/db* mice at 100-250 mg/kg p.o. with a duration of action > 27 h, while showing no adverse effects on body weight or food consumption. Potentially useful for the treatment of insulin-dependent and non-insulin-dependent diabetes mellitus. Other specifically claimed compounds from this series of piperazine derivatives include the following:



Compound	R1	R2	Formula
278193	H	2-pyrimidinyl	C ₁₈ H ₂₀ N ₆ O ₂ S
278194	Me	2-Pyr	C ₂₀ H ₂₃ N ₅ O ₂ S
278195	H	3-NO ₂ -Ph	C ₂₀ H ₂₁ N ₅ O ₄ S
278196	H	3-Me-Ph	C ₂₁ H ₂₄ N ₄ O ₂ S
278197	H	3-CF ₃ -4-Br-Ph	C ₂₁ H ₂₀ BrF ₃ N ₄ O ₂ S
278198	H	2-Naph	C ₂₄ H ₂₄ N ₄ O ₂ S
278199	H	3-MeO-Ph	C ₂₁ H ₂₄ N ₄ O ₃ S
278200	H	3,4-(Cl)2-Ph	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₂ S

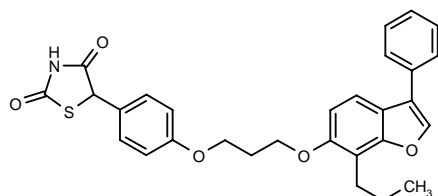
SOURCES – Lipha; Shaman.

REFERENCES

1. Bierter, D.E. et al. (Shaman Pharmaceuticals, Inc.;Lipha Santé) *Piperazine derivs. useful as hypoglycemic agents*. WO 9931096.

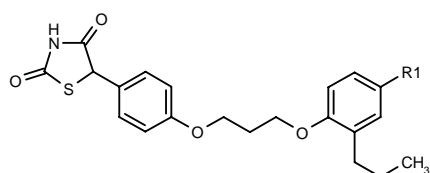
278357

5-[4-[3-(3-Phenyl-7-propylbenzofuran-6-yloxy)propoxy]-phenyl]thiazolidine-2,4-dione



C₂₉H₂₇N O₅ S; Mol wt: 501.6003

ACTION – Potent peroxisome proliferator-activated receptor (PPAR), particularly PPAR γ , agonist with potential in the treatment, control or prevention of diabetes, hyperglycemia, hyperlipidemia, atherosclerosis, obesity and vascular restenosis. Other specifically claimed substituted 5-aryl-2,4-thiazolidinediones include the following:



Compound	R1	Formula
278358	OPh	C ₂₇ H ₂₇ NO ₅ S
278359	4-F-Ph	C ₂₇ H ₂₆ FNO ₄ S

SOURCE – Merck & Co.

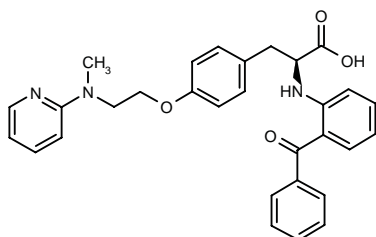
REFERENCES

1. Sahoo, S.P. et al. (Merck & Co., Inc.) *Arylthiazolidinedione derivs.* WO 9932465.

GW-1929**278223**

2(S)-(2-Benzoylanilino)-3-[4-[2-[N-methyl-N-(2-pyridinyl)-amino]ethoxy]phenyl]propionic acid

N-(2-Benzoylphenyl)-O-[2-[N-methyl-N-(2-pyridinyl)-amino]ethyl]-L-tyrosine



C₃₀H₂₉N₃O₄; Mol wt: 495.5761

Yellow solid.

ACTION – Antidiabetic agent, an *N*-aryl tyrosine activator of the peroxisome proliferator-activated receptor PPAR γ (pK_i = 8.85) with high selectivity over PPAR α and PPAR δ subtypes, as demonstrated in binding experiments (pK_i < 5.5 and 6.15, respectively) and a functional transfection

assay in CV-1 cells, where it was able to activate only the PPAR γ subtype (pEC₅₀ = 8.04). Compound was able to promote the differentiation of CH3H10T1/2 stem cells to adipocytes (pEC₅₀ = 7.74, lipogenesis assay) and showed antihyperglycemic and antihyperlipidemic effects in two *in vivo* models of type II diabetes. In *db/db* mice and in Zucker diabetic rats, compound given at a dose of 5 mg/kg p.o. for 14 days reduced postprandial plasma glucose (58 and 68%, respectively), serum triglycerides (61 and 87%, respectively) and nonesterified free fatty acids (38 and 73%, respectively), and significantly increased whole-body insulin sensitivity in Zucker diabetic rats. Treatment with compound significantly improved β -cell secretory function in response to glucose challenge and preserved pancreatic islet morphology and β -cell insulin immunostaining in Zucker rats. It was 2 orders of magnitude more potent than troglitazone both *in vitro* and *in vivo*.

SOURCE – Glaxo Wellcome.

REFERENCES

1. Willson, T.M. et al. (Glaxo Wellcome plc) *Substd. 4-hydroxy-phenylalkanoic acid derivs. with agonist activity to PPAR- γ* EP 888317, WO 9731907.

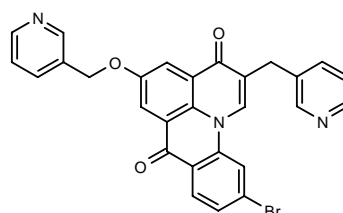
2. Brown, K.K. et al. *A novel N-aryl tyrosine activator of peroxisome proliferator-activated receptor- γ reverses the diabetic phenotype of the Zucker diabetic fatty rat.* Diabetes 1999, 48(7): 1415.

3. Henke, B.R. et al. *N-(2-Benzoylphenyl)-L-tyrosine PPAR γ agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents.* J Med Chem 1998, 41(25): 5020.

TREATMENT OF MALE SEXUAL DYSFUNCTION

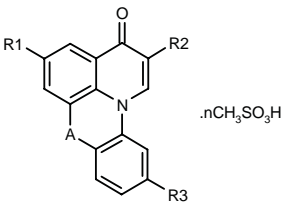
278510

10-Bromo-5-(3-pyridinylmethoxy)-2-(3-pyridinylmethyl)-3*H*,7*H*-pyrido[3,2,1-*de*]acridine-3,7-dione



C₂₈H₁₈Br N₃ O₃; Mol wt: 524.3722

ACTION – Potent and selective inhibitor of cGMP-phosphodiesterases (cGMP-PDE) with high activity against PDE5 and somewhat lower activity against PDE6, but little activity against PDE3 and PDE1. It is thus expected to be particularly useful in the treatment and/or prevention of pulmonary hypertension, ischemic heart disease, erectile dysfunction and female sexual dysfunction. Other exemplified fused tetracyclic compounds are:



Compound	R1	R2	A	R3	n	Formula
278512	H	3-Pyr-CH2	-O-	H	0	C ₂₁ H ₁₄ N ₂ O ₂
278513	H	CH2Ph	-N(Ac)-	H	0	C ₂₄ H ₁₈ N ₂ O ₂
278514	H	H	-NH-	H	0	C ₁₅ H ₁₀ N ₂ O
278515	H	3-Pyr-CH2	-CO-	H	0	C ₂₂ H ₁₄ N ₂ O ₂
278516	H	CH2Ph	bond	H	0	C ₂₁ H ₁₄ N ₂ O
278517	O(CH2)3OH	3-Pyr-CH2	-CO-	Br	0	C ₂₅ H ₁₈ BrN ₂ O ₄
278518	3-Pyr-CH2O	3-Pyr-CH2	-S-	Br	0	C ₂₇ H ₁₈ BrN ₃ O ₂ S
278519	4-Pyr-CH2O	3-Pyr-CH2	-S-	Br	0	C ₂₇ H ₁₈ BrN ₃ O ₂ S
278520	1,2,3-benzotriazol-1-yl	3-Pyr-CH2	-S-	Br	0	C ₂₈ H ₁₈ BrN ₅ O ₂ S
278521	3-Pyr-CH2O	3-Pyr-CH2	-S-	Br	2	C ₂₇ H ₁₈ BrN ₃ O ₂ S.2CH ₄ O ₃ S

SOURCE – Mochida.

REFERENCES

1. Ohashi, M. et al. (Mochida Pharmaceutical Co., Ltd.) *Novel cpds. having cGMP-PDE inhibitory effect.* WO 9928319.

WEIGE

276523

Chinese herbal medicine whose main bioactive constituent is dehydrocorydaline*

ACTION – Chinese herbal medicine for the treatment of male erectile dysfunction proven to improve erectile function in rats with higher efficacy and lower toxicity than sildenafil. Compound, like sildenafil, appeared to act by increasing cGMP levels in trabecular smooth muscle cells via inhibition of phosphodiesterase type 5 (PDE5) activity. In a double-blind clinical trial in 308 male patients with erectile dysfunction, compound was seen to improve sexual performance and satisfaction with sex life.

SOURCE – Shenyang Feilong Health Products.

REFERENCES

1. Wang, X.-W. *Weige.* Drugs Fut 1999, 24(7): 0747.

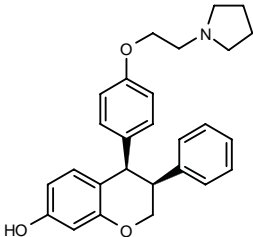
*Drug Data Rep 1990, 012 (03): 0212.

TREATMENT OF GYNECOLOGICAL DISORDERS

NNC-45-0781*

268276

(-)-cis-3-Phenyl-4-[4-[2-(1-pyrrolidiny)ethoxy]phenyl]-3,4-dihydro-2H-1-benzopyran-7-ol



C27 H29 N O3; Mol wt: 415.5301

ACTION – Third-generation selective estrogen receptor modulator (SERM), a nonsteroidal estrogen proven to produce conditioned taste aversion learning after a single injection (5-105 mg/kg) in gonadectomized rats.

SOURCE – Novo Nordisk.

REFERENCES

1. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel (-)-enantiomers of cis-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes.* EP 937057, WO 9818771.

2. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel cis-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes.* EP 937060, WO 9818776.

3. De Beun, R. and Jensen, T.N. *Dose- and sex-dependent conditioned taste aversions produced by nonsteroidal estrogen receptor ligands in rats.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PT66.

4. Zhou, W. et al. *Selective estrogen receptor modulator effects in rat brain.* 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P1-468.

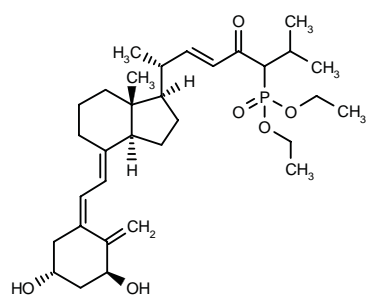
*Identified compound 268276 (see 265110) Drug Data Report 1998, 020(09): 0785.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

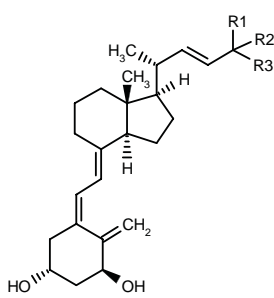
278102

22,23(E)-Didehydro-24a-(diethoxyphosphoryl)-1(S)-hydroxy-24-oxo-24a-homovitamin D₃



C32 H51 O6 P; Mol wt: 562.7229

ACTION – Antiproliferative agent, a vitamin D derivative with 10-fold higher affinity for the vitamin D receptor and 58-fold more potent differentiation-inducing activity in HL-60 cells compared to calcitriol, while showing > 300-fold lower hypercalcemic activity than the latter. Compound is reported to possess improved metabolic stability as compared to structurally related compounds. Potentially useful for the treatment of hyperproliferative disorders such as psoriasis, acne and cancer, as well as osteoporosis, autoimmune, inflammatory and neuro-degenerative disorders. Within this series of phosphorus-containing vitamin D derivatives, the following are also included:



Compound	R1	R2	R3	Formula
278103	-O-		CH(i-Pr)PO(OMe)2	C ₃₀ H ₄₇ O ₆ P
278104	-O-		CH(i-Pr)PO(O-i-Pr)2	C ₃₄ H ₅₅ O ₆ P
278105	PO(OEt)2	H	CH(i-Pr)PO(OEt)2	C ₃₆ H ₆₂ O ₈ P ₂
278106	-O-		C(Me)2PO(OEt)2	C ₃₁ H ₄₉ O ₆ P
278107	-O-		C(Et)2PO(OEt)2	C ₃₃ H ₅₃ O ₆ P
278108	i-Pr	(R)-OH	PO(O-i-Pr)2	C ₃₃ H ₅₅ O ₆ P

SOURCE – Schering AG.

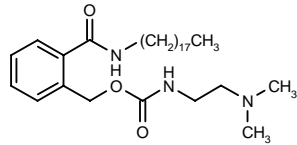
REFERENCES

1. Steinmeyer, A. et al. (Schering AG) *Vitamin D derivs. with phosphorous atoms in the side chains*. DE 19758119, EP 927721, WO 9931112.

HAIR GROWTH STIMULANTS

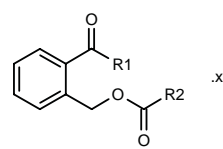
275836

N-[2-(Dimethylamino)ethyl]carbamic acid 2-(N-octadecyl-carbamoyl)benzyl ester



C31 H55 N3 O3; Mol wt: 517.7935

ACTION – Hair growth promoter associated with potent hair regrowth effects in mice following topical administration at a concentration of 0.1% w/v. Other compounds from this series of 1,2-di-substituted benzenecarbox-amides include the following:



Compound	R1	R2	X	Formula
275837	NHC18H37	NHCH2CH2N(Bu)2	HCl	C ₃₇ H ₆₇ N ₃ O ₃ .HCl
275838	NHC18H37	NHCH2CH2N(i-Pr)2	HCl	C ₃₅ H ₆₃ N ₃ O ₃ .HCl
275839	NHC18H37	4-Me-1-Piz		C ₃₂ H ₅₅ N ₃ O ₃
275840	4-Me-1-Piz	NHC18H37		C ₃₂ H ₅₅ N ₃ O ₃
275841	NH(CH2)17CH3	NH(CH2)3N(Bu)2	HCl	C ₃₈ H ₆₉ N ₃ O ₃ .HCl

SOURCE – Shiseido.

REFERENCES

1. Fukunishi, H. et al. (Shiseido Co. Ltd.) *1,2-Di-substd. benzenecarboxamide deriv., hair growth promoter and external compsn. for skin using the same*. EP 911320.

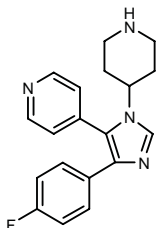
TOPICAL ANTIINFLAMMATORY AGENTS

SB-235699

277465

4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1*H*-imidazol-5-yl]pyridine

HEP-689



C19 H19 F N4; Mol wt: 322.3851

ACTION – Antiinflammatory agent, a potent and selective inhibitor of CSBP/p38 mitogen-activated protein (MAP) kinase, possessing topical antiinflammatory activity comparable to betamethasone in three murine models of skin inflammation. Compound inhibited both edema formation and polymorphonuclear leukocyte infiltration in oxazolone-induced contact sensitivity and TPA-induced chronic skin inflammation, and it decreased tissue IL-1 β , interferon gamma and IL-4 content in chronic oxazolone-induced ear dermatitis. Potentially useful for the treatment of skin disorders such as eczema, atopic dermatitis and psoriasis.

SOURCES – Leo; SmithKline Beecham.

REFERENCES

1. Adams, J.L. et al. (SmithKline Beecham Corp.) *Pyridyl imidazole cpds. and compsns.* US 5670527.
2. Adams, J.L. et al. (SmithKline Beecham plc) *Certain 1,4,5-tri-substd. imidazole cpds. useful as cytokine.* EP 809499, JP 98512555, US 5593992, WO 9621452.
3. Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries.* EP 889888, WO 9735856.
4. Aaes, H. et al. *Topical antiinflammatory activities of HEP689 in 3 murine models of dermatitis.* Mediators Inflamm 1999, 8(Suppl. 1): Abst P-11-11.

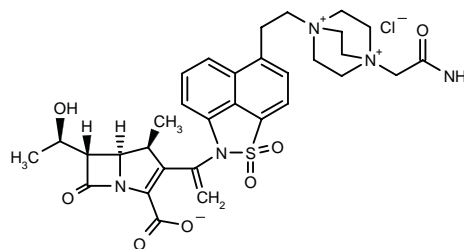
ANTIINFECTIVE THERAPY

ANTIBIOTICS

275774

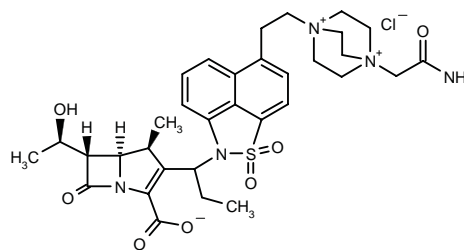
(1*S*,5*R*,6*S*)-2-[1-[6-[2-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]oct-1-yl]ethyl]-2*H*-naphtho[1,8-*cd*]-isothiazol-2-yl]vinyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylate *S,S*-dioxide chloride

(4*S*,5*R*,6*S*)-3-[1-[6-[2-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]oct-1-yl]ethyl]-1,1-dioxo-1 λ ⁶-2*H*-naphtho[1,8-*cd*]isothiazol-2-yl]vinyl]-6-[1(*R*)-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate chloride



C32 H38 Cl N5 O7 S; Mol wt: 672.1992

ACTION – Carbapenem antibiotic reported to be useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Another specifically claimed compound from this series of carbapenem derivatives is:



275775: C33 H42 Cl N5 O7 S

SOURCE – Merck & Co.

REFERENCES

1. Blizzard, T.A. and Ratcliffe, R.W. (Merck & Co., Inc.) *Antibacterial carbapenems, compsns. and methods of treatment.* WO 9918954.

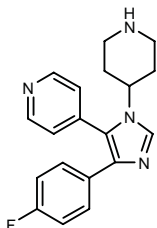
TOPICAL ANTIINFLAMMATORY AGENTS

SB-235699

277465

4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1*H*-imidazol-5-yl]pyridine

HEP-689



C19 H19 F N4; Mol wt: 322.3851

ACTION – Antiinflammatory agent, a potent and selective inhibitor of CSBP/p38 mitogen-activated protein (MAP) kinase, possessing topical antiinflammatory activity comparable to betamethasone in three murine models of skin inflammation. Compound inhibited both edema formation and polymorphonuclear leukocyte infiltration in oxazolone-induced contact sensitivity and TPA-induced chronic skin inflammation, and it decreased tissue IL-1 β , interferon gamma and IL-4 content in chronic oxazolone-induced ear dermatitis. Potentially useful for the treatment of skin disorders such as eczema, atopic dermatitis and psoriasis.

SOURCES – Leo; SmithKline Beecham.

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1. Adams, J.L. et al. (SmithKline Beecham Corp.) *Pyridyl imidazole cpds. and compsns.* US 5670527.
2. Adams, J.L. et al. (SmithKline Beecham plc) *Certain 1,4,5-tri-substd. imidazole cpds. useful as cytokine.* EP 809499, JP 98512555, US 5593992, WO 9621452.
3. Feuerstein, G.Z. (SmithKline Beecham plc) *Novel treatment for CNS injuries.* EP 889888, WO 9735856.
4. Aaes, H. et al. *Topical antiinflammatory activities of HEP689 in 3 murine models of dermatitis.* *Mediators Inflamm* 1999, 8(Suppl. 1): Abst P-11-11.

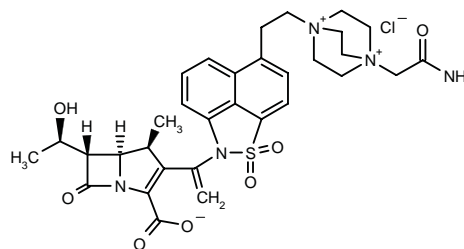
ANTIINFECTIVE THERAPY

ANTIBIOTICS

275774

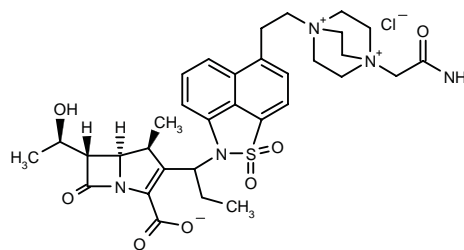
(1*S*,5*R*,6*S*)-2-[1-[6-[2-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]oct-1-yl]ethyl]-2*H*-naphtho[1,8-*cd*]-isothiazol-2-yl]vinyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylate *S,S*-dioxide chloride

(4*S*,5*R*,6*S*)-3-[1-[6-[2-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]oct-1-yl]ethyl]-1,1-dioxo-1 λ ⁶-2*H*-naphtho[1,8-*cd*]isothiazol-2-yl]vinyl]-6-[1(*R*)-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate chloride



C32 H38 Cl N5 O7 S; Mol wt: 672.1992

ACTION – Carbapenem antibiotic reported to be useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Another specifically claimed compound from this series of carbapenem derivatives is:



275775: C33 H42 Cl N5 O7 S

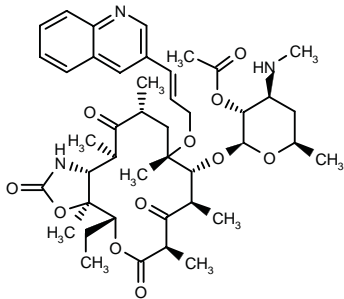
SOURCE – Merck & Co.

REFERENCES

1. Blizzard, T.A. and Ratcliffe, R.W. (Merck & Co., Inc.) *Antibacterial carbapenems, compsns. and methods of treatment.* WO 9918954.

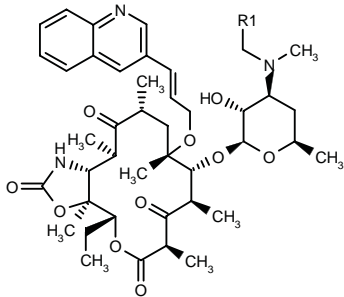
275842

2'-O-Acetyl-11-amino-3'-N-demethyl-11-deoxy-3-des(hexopyranosyloxy)-3-oxo-6-O-[3-(3-quinoliny)-2(E)-propenyl]erythromycin A 11-N,12-O-cyclic carbamate



C43 H59 N3 O11; Mol wt: 793.9491

ACTION – Macrolide antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* A5177 (MIC = 0.2 µg/ml vs. 3.1 µg/ml for erythromycin A), *Streptococcus pyogenes* PIU 2548 (MIC = 0.39 µg/ml vs. 6.2 µg/ml for erythromycin A), *Streptococcus pneumoniae* 5649 (MIC = 0.5 µg/ml vs. 16 µg/ml for erythromycin A) and *Escherichia coli* SS (MIC = 0.39 µg/ml vs. 0.78 µg/ml for erythromycin A). Other compounds from this series of 3'-N-modified 6-O-substituted erythromycin ketolide derivatives include the following:



Compound	R1	Formula
275843	vinyl	C ₄₄ H ₆₁ N ₃ O ₁₀
275844	CH2F	C ₄₃ H ₆₀ FN ₃ O ₁₀
275845	CH=CHPh	C ₅₀ H ₆₅ N ₃ O ₁₀
275846	C(CO2Me)=CH2	C ₄₆ H ₆₃ N ₃ O ₁₂
275847	C(Me)=CH2	C ₄₅ H ₆₃ N ₃ O ₁₀

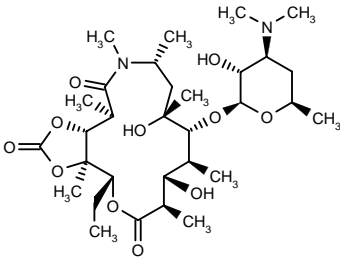
SOURCE – Abbott.

REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) 3'-N-Modified 6-O-substd. erythromycin ketolide derivs. having antibacterial activity. WO 9916779.

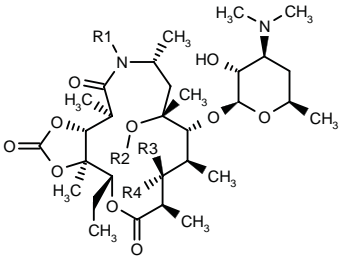
275948

8a-Aza-3-des(hexopyranosyl)-8a-methyl-8a-homo-erythromycin A 11-O,12-O-cyclic carbonate



C31 H54 N2 O11; Mol wt: 630.7706

ACTION – 8a-Azalide antibiotic structurally related to erythromycin A, active against Gram-positive and Gram-negative bacteria. Other specifically claimed compounds from this series of 8a-azalides include the following:



Compound	R1	R2	R3	R4	Formula
275949	-CH2-		OAc	H	C ₃₃ H ₅₄ N ₂ O ₁₂
275951	-CH2-		OCH2OCH2CH2OMe	H	C ₃₅ H ₆₀ N ₂ O ₁₃
275952	-CH2-		OCH2OMe	H	C ₃₃ H ₅₆ N ₂ O ₁₂
275953	-CO-		OH	H	C ₃₁ H ₅₀ N ₂ O ₁₂
275955	-CO-		H	H	C ₃₁ H ₅₀ N ₂ O ₁₁
275958	-CH2-		H	H	C ₃₁ H ₅₂ N ₂ O ₁₀
275959	-CH2-		OCS2Me	H	C ₃₃ H ₅₄ N ₂ O ₁₁ S ₂
275960	H	H	H	H	C ₃₀ H ₅₂ N ₂ O ₁₀
275961	Me	H	H	H	C ₃₁ H ₅₄ N ₂ O ₁₀
275962	-CH2-		-O-		C ₃₁ H ₅₀ N ₂ O ₁₁
276012	-CO-		-O-		C ₃₁ H ₄₈ N ₂ O ₁₂

SOURCE – Merck & Co.

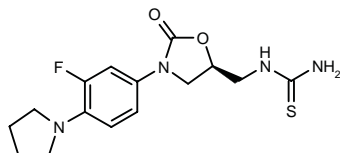
REFERENCES

1. Blizzard, T.A. et al. (Merck & Co., Inc.) 8a-Azalides, compsns. containing such cpds. and methods of treatment. WO 9919331.

ANTIBACTERIAL DRUGS

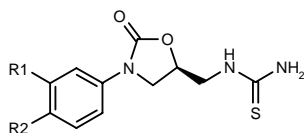
275922

N-[3-[3-Fluoro-4-(1-pyrrolidinyl)phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thiourea



C15 H19 F N4 O2 S; Mol wt: 338.4051

ACTION – Oxazolidinone antibacterial agent with activity against Gram-positive bacteria such as *Staphylococcus aureus* FDA 209P JC-1 (MIC = 0.39 µg/ml), methicillin-resistant *S. aureus* HPC1336 (MIC = 0.39 µg/ml), *Enterococcus faecalis* HPC975 (MIC = 0.39 µg/ml) and *Bacillus subtilis* ATCC 6633 (MIC = 0.20 µg/ml or less), being more potent than ciprofloxacin (MIC = 0.39, > 100, > 100 and 0.05 µg/ml, respectively). Other compounds from this series of thiourea derivatives include the following:



Compound	R1	R2	Formula
275923	F	OCH2CH2OMe	C ₁₄ H ₁₈ FN ₃ O ₄ S
275964	F	4-thiomorpholinyl	C ₁₅ H ₁₉ FN ₄ O ₂ S ₂
275966	F	4-morpholinyl	C ₁₅ H ₁₉ FN ₄ O ₃ S
275968	H	Ac	C ₁₃ H ₁₅ N ₃ O ₃ S

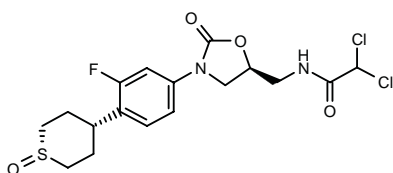
SOURCE – Hokuriku.

REFERENCES

1. Yoshida, T. et al. (Hokuriku Seiyaku Co., Ltd.) *Thiourea derivs.* JP 99158164, WO 9912914.

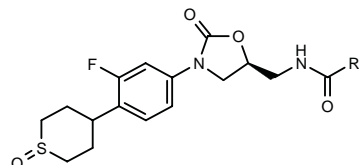
277818

trans-2,2-Dichloro-*N*-[3-[3-fluoro-4-(1-oxidoperhydrothiopyran-4-yl)phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]-acetamide



C17 H19 Cl2 F N2 O4 S; Mol wt: 437.3171

ACTION – Phenylloxazolidinone antibacterial agent found to be an unexpectedly weak inhibitor of human monoamine oxidase (MAO), indicating minimal or negligible potential for drug–drug interactions. It inhibited the growth of *Staphylococcus aureus* UC No. 9212 and *Haemophilus influenzae* 30063 with MIC values of 1 and 2 µg/ml, respectively, and it had a K_i for human MAO-A of 396 µM. Other specifically claimed *S*-oxide tetrahydrothiopyran phenylloxazolidinones are:



Compound	R1	Isomer	Formula
277819	Me	(-)-cis	C ₁₇ H ₂₁ FN ₂ O ₄ S
277820	Et	(-)-cis	C ₁₈ H ₂₃ FN ₂ O ₄ S
277821	cyclopropyl	(-)-cis	C ₁₉ H ₂₃ FN ₂ O ₄ S
277822	CH(Cl)2	cis	C ₁₇ H ₁₉ Cl ₂ FN ₂ O ₄ S
277823	Et	(-)-trans	C ₁₈ H ₂₃ FN ₂ O ₄ S
277824	cyclopropyl	(-)-trans	C ₁₉ H ₂₃ FN ₂ O ₄ S

SOURCE – Pharmacia & Upjohn.

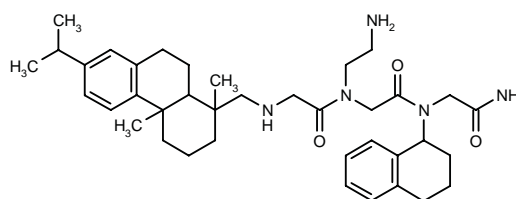
REFERENCES

1. Poel, T.-J. et al. (Pharmacia & Upjohn Co.) *S*-Oxide and *S,S*-dioxide tetrahydrothiopyran phenylloxazolidinones. WO 9929688.

CHIR-29498

278221

N-(2-Aminoethyl)-*N*-[*N*-(carbamoylmethyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)carbamoylmethyl]-2-(1,4a-dimethyl-7-isopropyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ylmethylamino)acetamide



C38 H55 N5 O3; Mol wt: 629.8845

ACTION – Peptoid antibacterial agent active in the range of 3-12 µg/ml against a panel of Gram-positive and Gram-negative bacteria including both drug-sensitive and multidrug-resistant isolates. Compound showed rapid bactericidal activity against *Staphylococcus aureus*, via a mechanism independent of protein synthesis and probably due to a membrane interaction. In *S. aureus*-infected mice, at doses of 10 and 30 mg/kg i.p. given immediately after infection it produced 100% survival; therapeutic efficacy was also observed when it was administered 110 min after infection (50% protection at 30 mg/kg i.p.). Hemolysis was observed at high concentrations and toxicity was noted at high doses (LD₅₀ = 60 mg/kg i.p. in mice).

SOURCE – Chiron.

REFERENCES

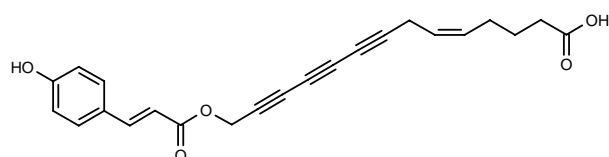
1. Goodson, B. et al. *Characterization of novel antimicrobial peptoids*. *Antimicrob Agents Chemother* 1999, 43(6): 1429.

2. Ng, S. et al. *Combinatorial discovery process yields antimicrobial peptoids*. *Bioorg Med Chem* 1999, 7(9): 1781.

CINNATRIACETIN A

277755

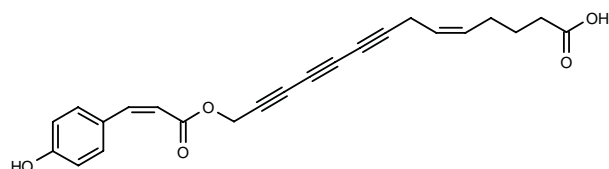
14-[3-(4-Hydroxyphenyl)-2(*E*)-propenoyloxy]tetradec-5(*Z*)-ene-8,10,12-triynoic acid



C₂₃ H₂₀ O₅; Mol wt: 376.4060

Pale brown powder.

ACTION – Antimicrobial agent extracted from the fruiting bodies of the Japanese mushroom *Fistulina hepatica*, proven active against Gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus* and *Bacillus coagulans*, but inactive against Gram-negative bacteria, yeasts and fungi. Another related compound is:



Cinnatriacetin B [277756]: C₂₃ H₂₀ O₅

SOURCE – House Foods.

REFERENCES

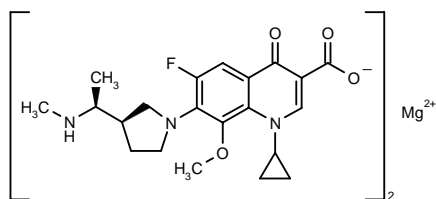
1. Tsuge, N. et al. *Cinnatriacetins A and B, new antibacterial triacetylene derivatives from the fruiting bodies of *Fistulina hepatica**. *J Antibiot* 1999, 52(6): 578.

PREMAFLOXACIN+ MAGNESIUM

Rec INN

277856

Di[1-cyclopropyl-6-fluoro-8-methoxy-7-[3(*R*)-[1(*S*)-(methylamino)ethyl]pyrrolidin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid] magnesium salt



2 C₂₁ H₂₅ F N₃ O₄ . Mg; Mol wt: 829.1920

ACTION – Magnesium–quinolone complex with relatively high solubility that may exist as a solution without a precipitate forming and without any need for additional acid or base additions to adjust pH; it may be administered as an s.c. or i.m. injection with little irritation at the injection site and is rapidly absorbed and taken up into the bloodstream. Preliminary animal studies indicate that the average blood levels of quinolone given with the Mg²⁺ solution are twice those in animals treated with free quinolone.

SOURCE – Pharmacia & Upjohn.

REFERENCES

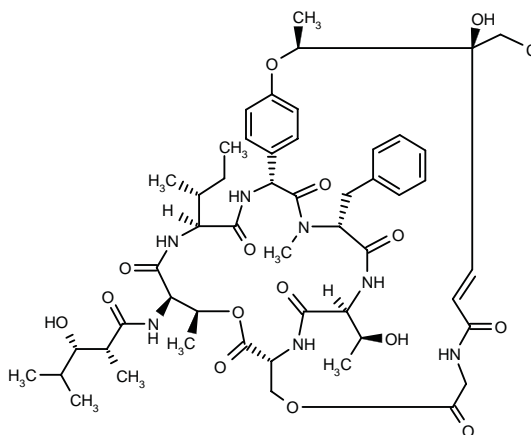
1. Barsuhn, K. et al. (Pharmacia & Upjohn Co.) *Magnesium quinolone antibiotics*. WO 9929322.

*Drug Data Rep 1995, 017(07): 0653.

SALINAMIDE B

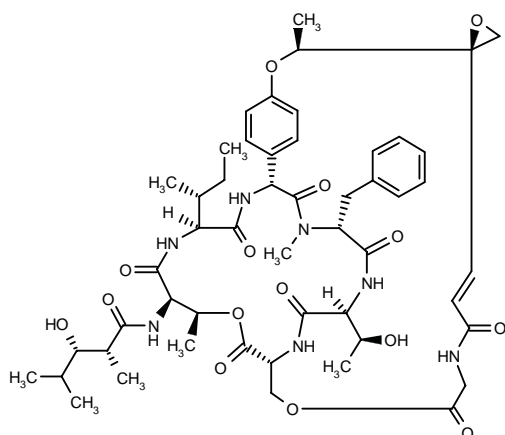
278190

[1*R*,7*S*,8*S*,9*E*,17*R*,20*S*,21*R*(2*S*,3*S*),24*S*(1*R*),29*R*,32*S*-(1*S*)]-29-Benzyl-8-(chloromethyl)-8-hydroxy-21-(3-hydroxy-2,4-dimethylpentanamido)-32-(1-hydroxyethyl)-7,20,28-trimethyl-24-(1-methylpropyl)[6,15,19]triox-[12,23,26,28,31,34]hexaazatricyclo[15.9.8.2^{2,5}]hexatriaconta-2,4,9,35-tetraene-11,14,18,22,25,27,30,33-octaone



C₅₁ H₇₀ Cl N₇ O₁₅; Mol wt: 1056.6010

ACTION – Antibacterial and antiinflammatory agent produced by fermentation of the marine actinomycete *Streptomyces* sp. CNB-091 in salt water-based media. Compound exhibited antibacterial activity against Gram-positive bacteria such as *Streptococcus pneumoniae* (MIC = 4 µg/ml) and *Streptococcus pyogenes* (MIC = 2 µg/ml), as well as topical antiinflammatory activity, as demonstrated in the PMA-induced mouse ear edema test by 42.0 and 81.0% inhibition of edema when applied topically at a dose of 10 and 50 µg/ear, respectively. Another compound isolated from the same source is:



Salinamide A [278191]: C₅₁ H₆₉ N₇ O₁₅

SOURCE – University of California, Oakland, Oakland, CA (US).

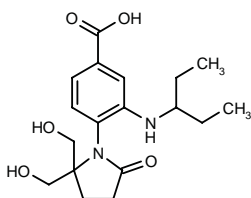
REFERENCES

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ANTIVIRAL DRUGS

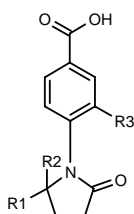
275971^{1,2,4}

4-[2,2-Bis(hydroxymethyl)-5-oxopyrrolidin-1-yl]-3-(1-ethylpropylamino)benzoic acid



C₁₈ H₂₆ N₂ O₅; Mol wt: 350.4124

ACTION – Antiviral agent for the treatment of influenza infections, a potent inhibitor of neuraminidase (IC₅₀ = 0.048 μM against enzyme from H1N9 influenza A strain) reported to be orally bioavailable. Other specifically claimed compounds from this series of pyrrolidin-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
275973 ^{1,2}	H	H	NHC(=NH)NH ₂	C ₁₂ H ₁₄ N ₄ O ₃
275975 ^{1,2,3}	CH ₂ OH	H	NHC(=NH)NH ₂	C ₁₃ H ₁₆ N ₄ O ₄
275976 ^{1,2}	CH ₂ NH ₂	H	NHC(=NH)NH ₂	C ₁₃ H ₁₇ N ₅ O ₃
275978 ^{1,2}	CH ₂ OH	CH ₂ OH	H	C ₁₃ H ₁₈ NO ₅

Compound	R1	R2	R3	Formula
275980 ^{1,2}	CH ₂ OH	CH ₂ OH	NHC(=NH)NH ₂	C ₁₄ H ₁₈ N ₄ O ₅
275985 ^{1,2}	H	H	NHCH(Et) ₂	C ₁₆ H ₂₂ N ₂ O ₃
275986 ¹	CH ₂ OH	CH ₂ OH	NHCH(Et)Pr	C ₁₉ H ₂₈ N ₂ O ₅
275987 ¹	CH ₂ OH	CH ₂ OH	NHCH(Pr) ₂	C ₂₀ H ₃₀ N ₂ O ₅
275988 ¹	CH ₂ OH	CH ₂ OH	N(Me)CH(Et) ₂	C ₁₉ H ₂₈ N ₂ O ₅
275989 ¹	CH ₂ OH	CH ₂ OH	NHPr	C ₁₆ H ₂₂ N ₂ O ₅
275990 ¹	CH ₂ OH	CH ₂ OH	NHC ₅ H ₁₁	C ₁₈ H ₂₆ N ₂ O ₅
275992 ¹	CH ₂ OH	CH ₂ OH	NHCOEt	C ₁₆ H ₂₀ N ₂ O ₆
275993 ¹	CH ₂ OH	CH ₂ OH	NHCOCH(Me)Et	C ₁₈ H ₂₄ N ₂ O ₆
275995 ¹	CH ₂ OH	CH ₂ OH	NHCOCH(Et) ₂	C ₁₉ H ₂₆ N ₂ O ₆
275996 ¹	CH ₂ NH ₂	CH ₂ OH	NHCOCH(Me)Et	C ₁₈ H ₂₅ N ₃ O ₅
275998 ¹	CH ₂ CH ₂ OH	CH ₂ OH	NHCOCH(Et) ₂	C ₂₀ H ₂₈ N ₂ O ₆

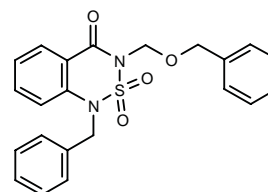
SOURCE – BioCryst.

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1. Brouillette, W.J. et al. (BioCryst Pharmaceuticals, Inc.) *Pyrrolidin-2-one cpds. and their use as neuraminidase inhibitors*. WO 9914191.
2. Atigadda, V.R. et al. *Potent inhibition of influenza sialidase by a benzoic acid containing a 2-pyrrolidinone substituent*. J Med Chem 1999, 42(13): 2332.
3. Brouillette, W.J. et al. *Design of benzoic acid inhibitors of influenza neuraminidase containing cyclic substitution for the N-acetyl grouping*. Bioorg Med Chem Lett 1999, 9(14): 1901.
4. Brouillette, W.J. et al. *New potent aromatic inhibitors of influenza virus sialidase*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 277.

276974

1-Benzyl-3-(benzyloxymethyl)-3,4-dihydro-1H-1,3-benzothiadiazin-4-one S,S-dioxide



C₂₂ H₂₀ N₂ O₄ S; Mol wt: 408.4760

ACTION – Antiviral agent active against human cytomegalovirus (IC₅₀ = 3.5 and 3.7 μg/ml, respectively, against AD-169 and Davis strains in HEL cells) and varicella-zoster virus (IC₅₀ = 3.0 μg/ml against YS/R strain thymidine kinase in HEL cells), with low cytotoxicity in uninfected cells (CC₅₀ > 40 μg/ml), and also against HIV-1 and HIV-2 (EC₅₀ = 15 and 20 μg/ml, respectively, in CEM cells) at concentrations 5-fold lower than cytotoxic concentrations (CC₅₀ = 100 μg/ml).

SOURCES – CSIC, Madrid (ES); Rega Institute for Medical Research, Leuven (BE).

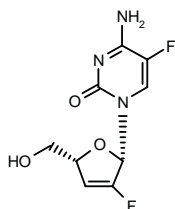
REFERENCES

1. Martinez, A. et al. *Benzothiadiazine dioxide acyclonucleosides as lead cpds. for the development of new agents against human cytomegalovirus and varicella-zoster virus infection*. Bioorg Med Chem Lett 1997, 7(8): 1031.
2. Martinez, A. et al. *Novel potential agents for human cytomegalovirus infection: Synthesis and antiviral activity evaluation of benzothiadiazine dioxide acyclonucleosides*. J Med Chem 1999, 42(7): 1145.

276977^{1,2,4}

1-(2,3-Dideoxy-2-fluoro-β-L-glycero-pent-2-enofuranosyl)-5-fluorocytosine

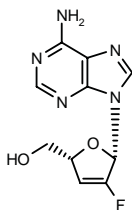
β-L-2'-Fd4FC



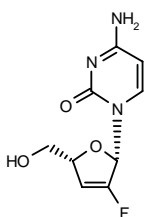
C₉ H₉ F₂ N₃ O₃; Mol wt: 245.1841

M.p. 202-5 °C, $[\alpha]_D -26.76^\circ$ (*c* 0.21, MeOH).

ACTION – Antiviral agent active against HIV-1 (EC_{50} = 0.17 μM in infected human peripheral blood mononuclear cells) and hepatitis B virus (HBV; EC_{50} = 0.225 μM in 2.2.15 cells; EC_{50} zidovudine > 10 μM); compound showed no significant cytotoxicity in PBMCs, Vero cells and CEM cells (IC_{50} > 100 μM). Other related L-nucleoside analogues include the following:



276978²⁻⁴: C₁₀ H₁₀ F N₅ O₂



277021⁴: C₉ H₁₀ F N₃ O₃

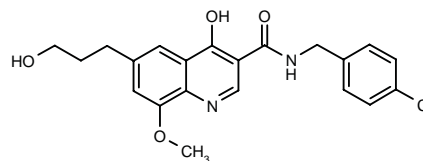
SOURCES – Emory University, Atlanta, GA (US); University of Georgia, Athens, GA (US); Yale University, New Haven, CT (US).

REFERENCES

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- Chen, S.-H. et al. *Synthesis and biological evaluation of a series of 2'-fluorinated-2',3'-dideoxy-2',3'-didehydro-(L)-nucleosides*. Bioorg Med Chem Lett 1998, 8(13): 1589.
- Choi, Y. et al. *Synthesis and anti-HIV activity of L-2'-fluoro-2',3'-unsaturated purine nucleosides*. Tetrahedron Lett 1998, 39(25): 4437.
- Lee, K. et al. *Synthesis and anti-HIV and anti-HBV activities of 2'-fluoro-2',3'-unsaturated L-nucleosides*. J Med Chem 1999, 42(7): 1320.

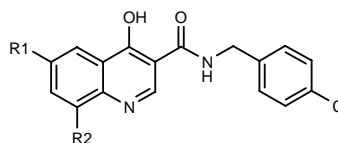
278255

N-(4-Chlorobenzyl)-4-hydroxy-6-(3-hydroxypropyl)-8-methoxyquinoline-3-carboxamide

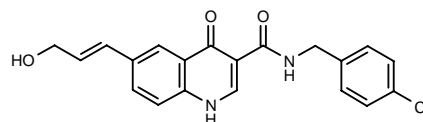


C₂₁ H₂₁ Cl N₂ O₄; Mol wt: 400.8599

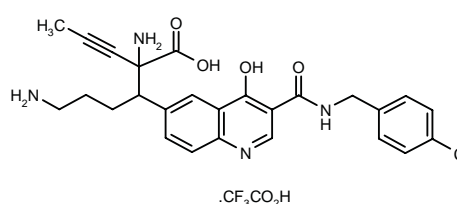
ACTION – Antiviral agent particularly useful for the treatment or prevention of herpesvirus infections, and especially human cytomegalovirus (CMV) infections. It had IC_{50} values for inhibition of CMV, varicella-zoster virus (VZV) and herpes simplex virus (HSV) polymerase of 0.27, 0.08 and 0.25 μM, respectively. Other specifically claimed 4-hydroxyquinoline-3-carboxamides and hydrazides are:



Compound	R1	R2	Formula
278256	(CH ₂) ₃ OH	F	C ₂₀ H ₁₈ ClFN ₂ O ₃
278257	ethynylene-CH ₂ OH	OMe	C ₂₁ H ₁₇ ClN ₂ O ₄
278259	MeOCH ₂ -ethynylene	OMe	C ₂₂ H ₁₉ ClN ₂ O ₄
278260	(CH ₂) ₃ OH	H	C ₂₀ H ₁₉ ClN ₂ O ₃
278261	ethynylene-CH ₂ OCO(CH ₂) ₆ -CON(Me)CH ₂ CH ₂ SO ₃ Na	H	C ₃₁ H ₃₃ ClN ₃ NaO ₈ S
278262	(CH ₂) ₃ OCO(CH ₂) ₆ -CON(Me)CH ₂ CH ₂ SO ₃ Na	H	C ₃₁ H ₃₇ ClN ₃ NaO ₈ S
278263	(CH ₂) ₃ OPO(OH) ₂	H	C ₂₀ H ₂₀ ClN ₂ O ₆ P
278268	2-thienyl	H	C ₂₁ H ₁₅ ClN ₂ O ₂ S
278270	CH ₂ OCH ₂ CH ₂ OH	H	C ₂₀ H ₁₉ ClN ₂ O ₄
278271	4-morpholinyl-CH ₂	H	C ₂₂ H ₂₂ ClN ₃ O ₃
278567	(CH ₂) ₃ OPO(OH)H	H	C ₂₀ H ₂₀ ClN ₂ O ₆ P



Compound	Isomer	Formula
278264	Z	C ₂₀ H ₁₇ ClN ₂ O ₃
278265	E	C ₂₀ H ₁₇ ClN ₂ O ₃



278266: C₂₆ H₂₇ Cl N₄ O₄ . C₂ H F₃ O₂

SOURCE – Pharmacia & Upjohn.

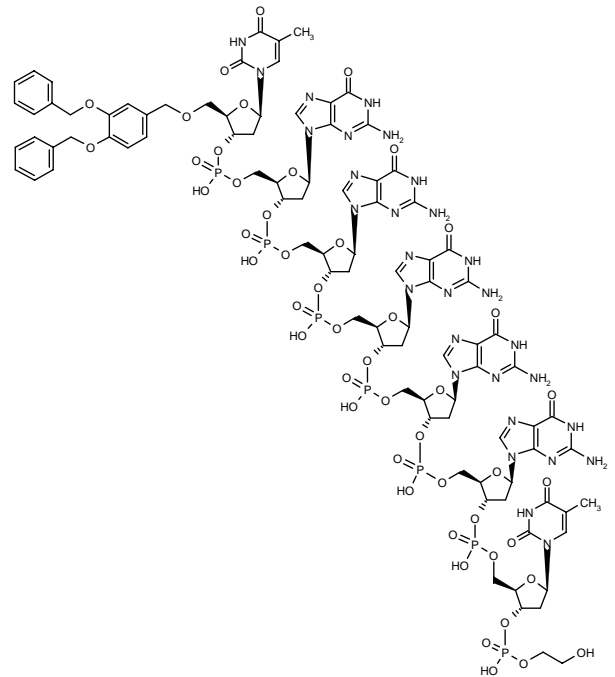
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AIDS MEDICINES

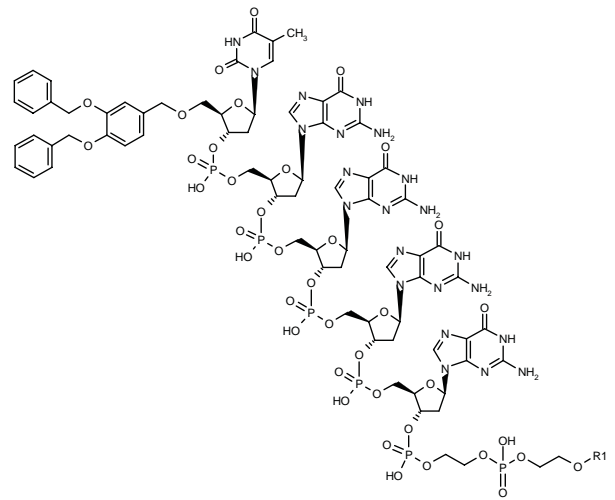
276750

2-[2'-Deoxy-5'-(3,4-dibenzyloxybenzyl)thymidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxy-3'-thymidylyl]ethanol

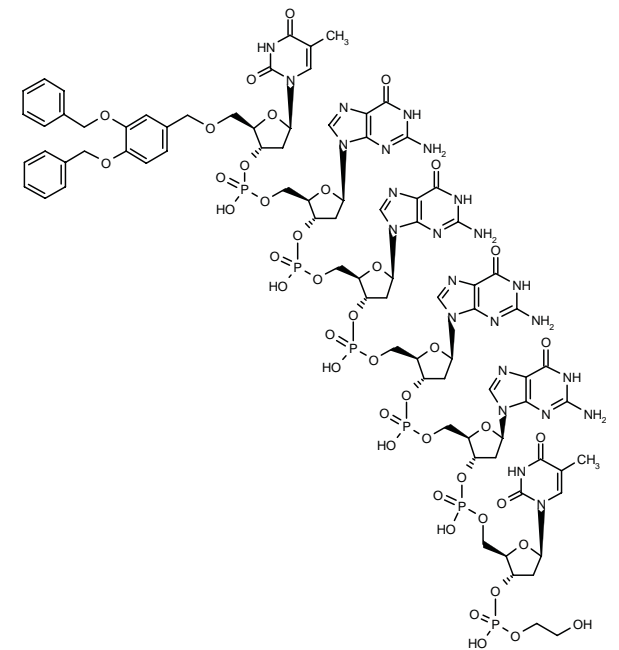


C93 H110 N29 O48 P7; Mol wt: 2618.8650

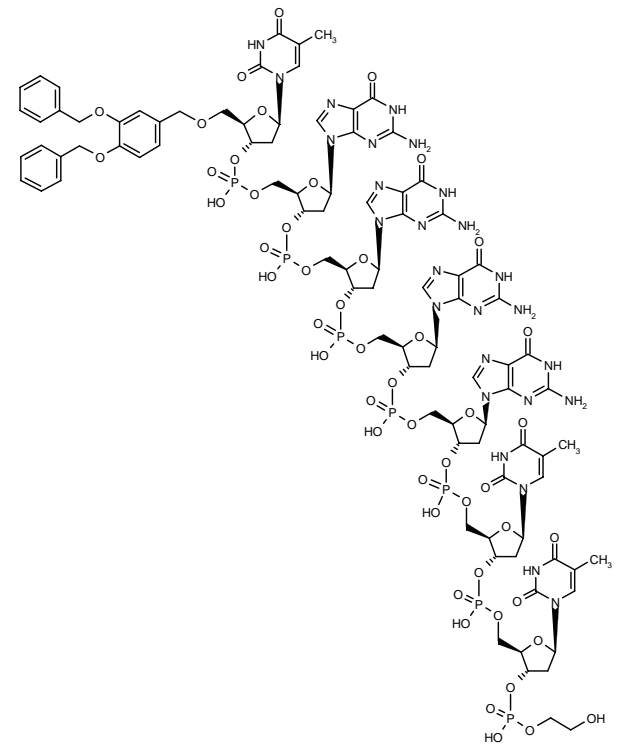
ACTION – Antiviral agent for AIDS with potent antiviral activity in HIV-1_{IIIB}-infected MT-4 cells (IC₅₀ = 0.16 µg/ml) and low cytotoxicity (CC₅₀ > 50 µg/ml). Other compounds from this series of modified oligodeoxyribonucleotides include the following:



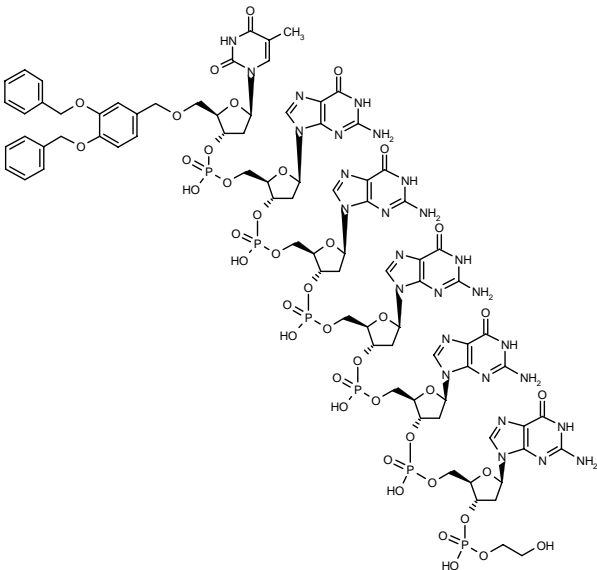
Compound	R1	Formula
276754	H	C ₇₅ H ₉₀ N ₂₂ O ₃₉ P ₆
276755	PO(OH)OCH ₂ CH ₂ OH	C ₇₇ H ₉₅ N ₂₂ O ₄₃ P ₇



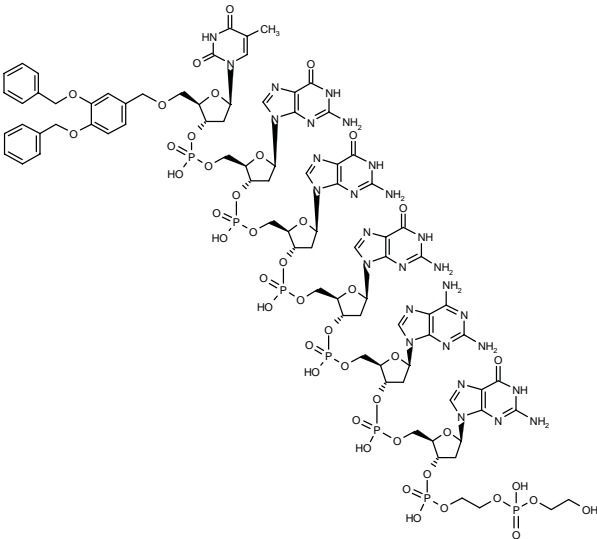
276751: C83 H98 N24 O42 P6



276752: C93 H111 N26 O49 P7



276753: C83 H97 N27 O41 P6



276756: C85 H103 N28 O44 P7

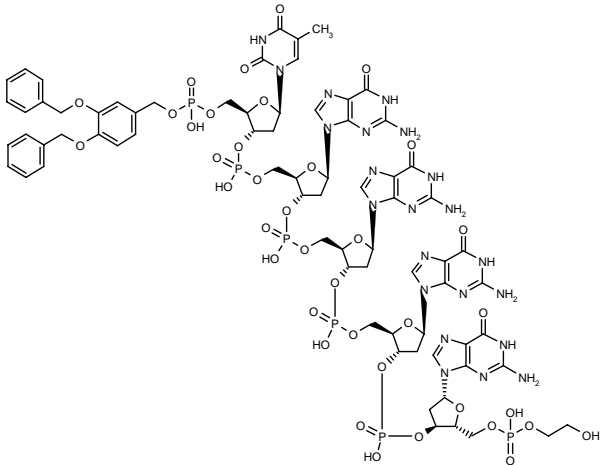
SOURCE – Sankyo.

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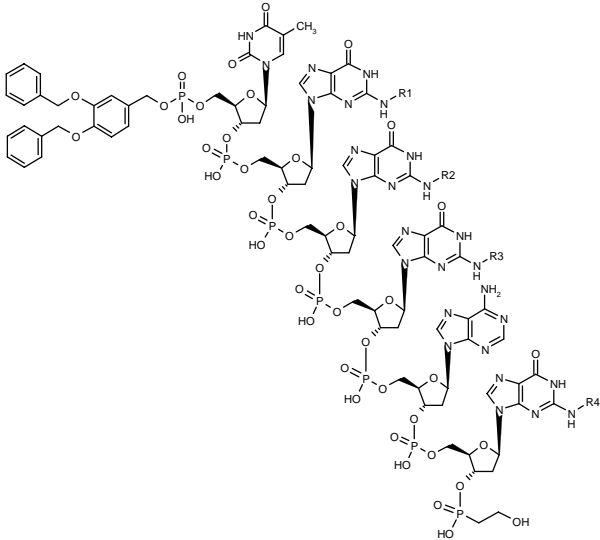
277664

5'-O-[3,4-Bis(benzyloxy)benzyl]-2'-deoxythymidyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→3')-2'-deoxy-5'-guanylic acid 5'-(2-hydroxyethyl) ester



C73 H86 N22 O38 P6; Mol wt: 2065.4420

ACTION – Antiviral agent for AIDS with potent antiviral activity in HIV-1_{IIIB}-infected MT-4 cells (IC₅₀ = 0.23 µg/ml) and low cytotoxicity (CC₅₀ > 50 µg/ml). Other compounds from this series of modified oligodeoxyribonucleotides include the following:



Compound	R1	R2	R3	R4	Formula
277665	Me	H	H	H	C ₈₄ H ₁₀₀ N ₂₇ O ₄₂ P ₇
277666	H	Me	H	H	C ₈₄ H ₁₀₀ N ₂₇ O ₄₂ P ₇
277667	H	H	Me	H	C ₈₄ H ₁₀₀ N ₂₇ O ₄₂ P ₇
277668	H	H	H	Me	C ₈₄ H ₁₀₀ N ₂₇ O ₄₂ P ₇
277669	Me	Me	Me	H	C ₈₆ H ₁₀₄ N ₂₇ O ₄₂ P ₇

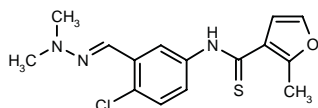
SOURCE – Sankyo.

REFERENCES

1. Koizumi, M. et al. (Sankyo Co., Ltd.) *Oligodeoxyribonucleotides containing modified nucleoside and the like.* JP 99199597, WO 9921874.

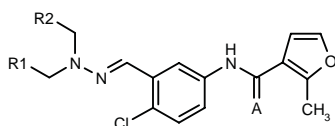
277838

N-[4-Chloro-3-(2,2-dimethylhydrazonomethyl)phenyl]-2-methylfuran-3-carbothioamide



C₁₅ H₁₆ Cl N₃ O S; Mol wt: 321.8304

ACTION – Anti-HIV agent with EC₅₀ values of 0.008 µg/ml against HIV-1_{IIIB} and values ranging from 0.040 µg/ml to < 2.00 µg/ml against reverse transcriptase mutant strains, as evaluated by inhibition of syncytium formation in infected CEM cells. Other exemplified hydrazones are:



Compound	R1	R2	A	Formula
277839	H	H	O	C ₁₅ H ₁₆ ClN ₃ O ₂
277840	-(CH ₂) ₂ -		O	C ₁₇ H ₁₈ ClN ₃ O ₂
277841	-(CH ₂) ₂ -		S	C ₁₇ H ₁₈ ClN ₃ OS

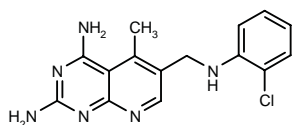
SOURCE – Uniroyal.

REFERENCES

1. Brouwer, W.G. and Osika, E.M. (Uniroyal Chemical Company, Inc.) *Anti-viral aromatic hydrazones*. US 5914351.

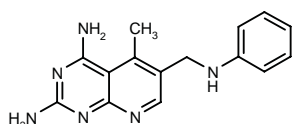
277847

6-(2-Chlorophenylaminomethyl)-5-methylpyrido[2,3-*d*]-pyrimidine-2,4-diamine



C₁₅ H₁₅ Cl N₆; Mol wt: 314.7785

ACTION – An inhibitor of dihydrofolate reductase (DHFR) with IC₅₀ values against enzyme from *Pneumocystis carinii* and *Toxoplasma gondii* of 47 and 7.1 nM, respectively, and good selectivity over rat liver DHFR (IC₅₀ = 88 nM), superior to that of trimetrexate and piritrexim. Compound strongly inhibited the growth of *T. gondii* in culture (IC₅₀ = 58 nM) and it also inhibited the growth of a variety of tumor cells *in vitro* with GI₅₀ values in the range of 1-100 nM. Potentially useful for the treatment of opportunistic infections in AIDS patients and also as an antitumor agent. Another related compound is:



277849: C₁₅ H₁₆ N₆

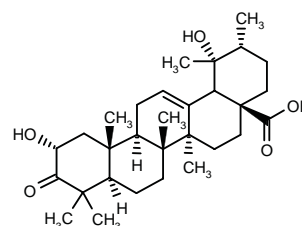
SOURCES – Duquesne University, Pittsburgh, PA (US); Indiana University, Indianapolis, IN (US).

REFERENCES

1. Gangjee, A. et al. *Pneumocystis carinii* and *Toxoplasma gondii* dihydrofolate reductase inhibitors and antitumor agents: Synthesis and biological activities of 2,4-diamino-5-methyl-6-[(monosubstituted anilino)methyl]-pyrido[2,3-*d*]pyrimidines. J Med Chem 1999, 42(13): 2447.

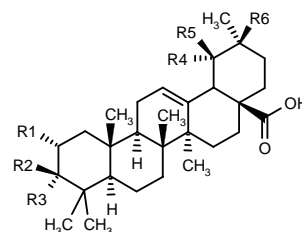
277910

(1*R*,2*R*,4*aR*,6*aS*,6*bR*,8*aR*,11*R*,12*aR*,12*bR*)-1,11-Dihydroxy-1,2,6*a*,6*b*,9,9,12*a*-heptamethyl-10-oxo-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,12*b*,13,14*b*-icosahydronicene-4*a*-carboxylic acid



C₃₀ H₄₆ O₅; Mol wt: 486.6884

ACTION – Anti-HIV triterpene isolated from a methanol extract of the plant *Geum japonicum* that acts by inhibiting retroviral protease; it inhibited HIV-1 protease by 72.19% at a concentration of 17.9 µg/ml. Other triterpenes isolated from the same source are:



Compound	R1	R2	R3	R4	R5	R6	Formula
277911	H	OH	H	H	Me	H	C ₃₀ H ₄₈ O ₃
277912	H	H	OAc	OH	Me	H	C ₃₂ H ₅₀ O ₅
277913	OH	OH	H	H	H	Me	C ₃₀ H ₄₈ O ₄

SOURCES – Dalhousie University, Halifax, NS (CA); National University of Singapore (SG).

REFERENCES

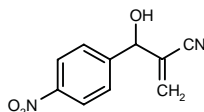
1. Xu, H.-X. et al. (Dalhousie University; National University of Singapore) *Retrovirus protease inhibitors*. US 5916919.

TREATMENT OF PROTOZOAL DISEASES

273695²

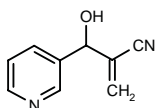
2-[Hydroxy(4-nitrophenyl)methyl]acrylonitrile

3-Hydroxy-2-methylene-3-(4-nitrophenyl)propionitrile



C₁₀ H₈ N₂ O₃; Mol wt: 204.1842

ACTION – Antimalarial agent proven to completely inhibit total parasite growth and schizont maturation of both wild-type and chloroquine-resistant *Plasmodium falciparum* at concentrations of 1-5 μ mol/well. *In vivo*, s.c. doses of 80-160 mg/kg were able to prolong the survival time of mice infected with *Plasmodium berghei* from 6.0 days in untreated controls to 12.8-14.4 days. Another related compound is:



273696^{1,2}: C₉ H₈ N₂ O

SOURCE – Indian Institute of Technology, Bombay (IN).

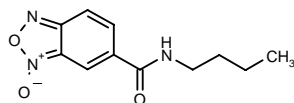
REFERENCES

1. Deane, P.O. et al. *Regio- and diastereoselectivity in the thiomethylation of α -(1-hydroxyalkyl)acrylate derivatives*. *Synth Commun* 1998, 28(14): 2601.

2. Kundu, M.K. et al. *Antimalarial activity of 3-hydroxyalkyl-2-methylene-propionic acid derivatives*. *Bioorg Med Chem Lett* 1999, 9(5): 731.

277077

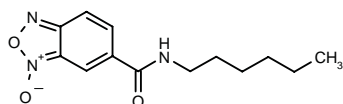
N-Butyl-2,1,3-benzoxadiazole-6-carboxamide 1-oxide



C₁₁ H₁₃ N₃ O₃; Mol wt: 235.2417

Yellow needles, m.p. 164-6 °C.

ACTION – Antiprotozoal agent shown to inhibit the growth of *Trypanosoma cruzi* epimastigotes (ID₅₀ = 10 μ M) with potency comparable to the reference drug nifurtimox (ID₅₀ = 2 μ M); cytotoxicity against mammalian fibroblasts was also comparable. Compound acts through a mechanism that involves N-oxide radical formation. Potentially useful for the treatment of chronic Chagas' disease. Another related compound is:



277087: C₁₃ H₁₇ N₃ O₃

SOURCES – Universidad de Chile, Santiago de Chile (CL); Universidad de la República, Montevideo (UY).

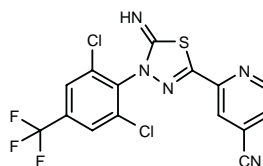
REFERENCES

1. Cerecetto, H. et al. *1,2,5-Oxadiazole N-oxide derivatives and related compounds as potential antitrypanosomal drugs: Structure-activity relationships*. *J Med Chem* 1999, 42(11): 1941.

TREATMENT OF HELMINTHIC DISEASES

277519

2-[4-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-5-imino-4,5-dihydro-1,3,4-thiadiazol-2-yl]pyridine-4-carbonitrile



C₁₅ H₆ Cl₂ F₃ N₅ S; Mol wt: 416.2134

White solid.

ACTION – Potential anthelmintic agent that binds to the AF-2 neuropeptide receptor in nematode tissue (IC₅₀ = 10 nM).

The AF-2 receptor is present in *Ascaris suum* and other nematodes and has been shown to induce excitation and spastic paralysis *in vitro* in neuromuscular strips.

SOURCE – Pharmacia & Upjohn.

REFERENCES

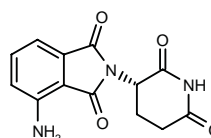
1. Lee, B.H. et al. *Synthesis and biological activity of anthelmintic thiadiazoles using an AF-2 receptor binding assay*. *Bioorg Med Chem Lett* 1999, 9(12): 1727.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

277394

4-Amino-2-[2,6-dioxopiperidin-3(S)-yl]-1H-isoindole-1,3(2H)-dione



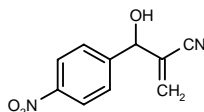
C₁₃ H₁₁ N₃ O₄; Mol wt: 273.2469

TREATMENT OF PROTOZOAL DISEASES

273695²

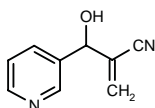
2-[Hydroxy(4-nitrophenyl)methyl]acrylonitrile

3-Hydroxy-2-methylene-3-(4-nitrophenyl)propionitrile



C₁₀ H₈ N₂ O₃; Mol wt: 204.1842

ACTION – Antimalarial agent proven to completely inhibit total parasite growth and schizont maturation of both wild-type and chloroquine-resistant *Plasmodium falciparum* at concentrations of 1-5 μ mol/well. *In vivo*, s.c. doses of 80-160 mg/kg were able to prolong the survival time of mice infected with *Plasmodium berghei* from 6.0 days in untreated controls to 12.8-14.4 days. Another related compound is:



273696^{1,2}: C₉ H₈ N₂ O

SOURCE – Indian Institute of Technology, Bombay (IN).

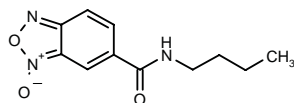
REFERENCES

1. Deane, P.O. et al. *Regio- and diastereoselectivity in the thiomethylation of α -(1-hydroxyalkyl)acrylate derivatives*. *Synth Commun* 1998, 28(14): 2601.

2. Kundu, M.K. et al. *Antimalarial activity of 3-hydroxyalkyl-2-methylene-propionic acid derivatives*. *Bioorg Med Chem Lett* 1999, 9(5): 731.

277077

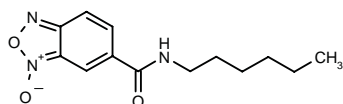
N-Butyl-2,1,3-benzoxadiazole-6-carboxamide 1-oxide



C₁₁ H₁₃ N₃ O₃; Mol wt: 235.2417

Yellow needles, m.p. 164-6 °C.

ACTION – Antiprotozoal agent shown to inhibit the growth of *Trypanosoma cruzi* epimastigotes (ID₅₀ = 10 μ M) with potency comparable to the reference drug nifurtimox (ID₅₀ = 2 μ M); cytotoxicity against mammalian fibroblasts was also comparable. Compound acts through a mechanism that involves N-oxide radical formation. Potentially useful for the treatment of chronic Chagas' disease. Another related compound is:



277087: C₁₃ H₁₇ N₃ O₃

SOURCES – Universidad de Chile, Santiago de Chile (CL); Universidad de la República, Montevideo (UY).

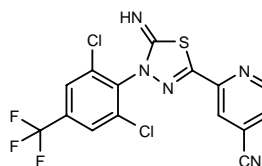
REFERENCES

1. Cerecetto, H. et al. *1,2,5-Oxadiazole N-oxide derivatives and related compounds as potential antitrypanosomal drugs: Structure-activity relationships*. *J Med Chem* 1999, 42(11): 1941.

TREATMENT OF HELMINTHIC DISEASES

277519

2-[4-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-5-imino-4,5-dihydro-1,3,4-thiadiazol-2-yl]pyridine-4-carbonitrile



C₁₅ H₆ Cl₂ F₃ N₅ S; Mol wt: 416.2134

White solid.

ACTION – Potential anthelmintic agent that binds to the AF-2 neuropeptide receptor in nematode tissue (IC₅₀ = 10 nM).

The AF-2 receptor is present in *Ascaris suum* and other nematodes and has been shown to induce excitation and spastic paralysis *in vitro* in neuromuscular strips.

SOURCE – Pharmacia & Upjohn.

REFERENCES

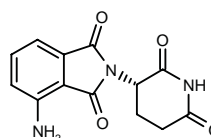
1. Lee, B.H. et al. *Synthesis and biological activity of anthelmintic thiadiazoles using an AF-2 receptor binding assay*. *Bioorg Med Chem Lett* 1999, 9(12): 1727.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

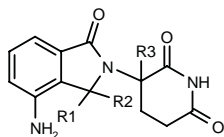
277394

4-Amino-2-[2,6-dioxopiperidin-3(S)-yl]-1H-isoindole-1,3(2H)-dione



C₁₃ H₁₁ N₃ O₄; Mol wt: 273.2469

ACTION – Potent and selective inhibitor of TNF- α production (IC_{50} = 3.9 and 14 nM, respectively, for inhibition of lipopolysaccharide-induced TNF- α production in human peripheral blood mononuclear cells [PBMCs] and whole blood), inactive against phosphodiesterase type 4 (PDE4; < 50% inhibition at 100 μ M). Potentially useful for the treatment of inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease. Other related thalidomide analogues are:



Compound	R1	R2	R3	Formula
277395	H	H	H	C ₁₃ H ₁₃ N ₃ O ₃
277396		-O-	Me	C ₁₄ H ₁₃ N ₃ O ₄

SOURCE – Celgene.

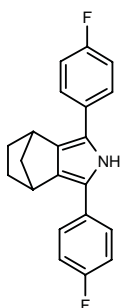
REFERENCES

1. Muller, G.W. et al. (Celgene Corp.) *Substd. 2-(2,6-dioxopiperidin-3-yl)-phthalimides and 1-oxoisindolines and method of reducing TNF α levels.* EP 925294, US 5635517, WO 9803502, WO 9854170.

2. Muller, G.W. et al. *Amino-substituted thalidomide analogs: Potent inhibitors of TNF- α production.* Bioorg Med Chem Lett 1999, 9(11): 1625.

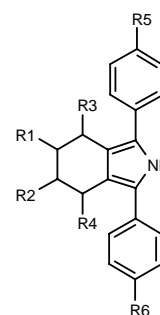
277416

1,3-Bis(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-4,7-methanoisindole

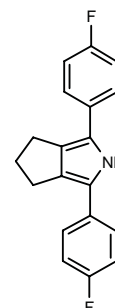


C₂₁ H₁₇ F₂ N; Mol wt: 321.3683

ACTION – Specific inhibitor of cyclooxygenase type 2 (COX-2), IL-1 β and inducible nitric oxide synthase (iNOS) proven to inhibit COX-1 and COX-2 in murine peritoneal macrophages stimulated with zymosan or lipopolysaccharide (LPS) with IC_{50} values of 0.1 and 0.001 μ M, respectively, as well as to inhibit the production of NO in LPS-stimulated murine peritoneal macrophages with an IC_{50} of 2.5 μ M. *In vivo*, it was effective in inhibiting prostaglandin production in the mouse carrageenan air pouch model, with an ED_{50} of 2.5 mg/kg p.o., and no evidence of gastric damage was detected at doses of up to 800 mg/kg p.o. Particularly useful in the treatment of rheumatic disorders such as arthrosis and rheumatoid arthritis, as well as atherosclerosis and cancer. Other specifically claimed pyrrole derivatives are:



Compound	R1=R2	R3	R4	R5=R6	Formula
277417	Me	H	H	H	C ₂₂ H ₂₃ N
277418	H	-CH ₂ -		H	C ₂₁ H ₁₉ N
277420	H	-(CH ₂) ₂ -		H	C ₂₂ H ₂₁ N
277421	H	H	H	F	C ₂₀ H ₁₇ F ₂ N



277419: C₁₉ H₁₅ F₂ N

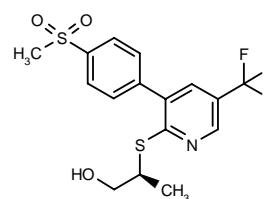
SOURCE – ADIR.

REFERENCES

1. De Nanteuil, G. et al. (ADIR et Cie.) *Pyrrole derivs., process for their preparation and pharmaceutical compsns. containing them.* CA 2254521, EP 921119, FR 2771412.

277518

2-(S)-[3-(4-Methylsulfonylphenyl)-5-(trifluoromethyl)pyridin-2-ylsulfanyl]propan-1-ol



C₁₆ H₁₆ F₃ N O₃ S₂; Mol wt: 391.4324

ACTION – Antiinflammatory agent, a potent cyclooxygenase type 2 (COX-2) inhibitor (IC_{50} = 0.14 μ M) with high selectivity over COX-1 (IC_{50} = 29 μ M). Compound showed good oral bioavailability (> 75%) and good efficacy in three models of inflammation in rats: carrageenan-induced paw edema (ED_{50} = 0.3 mg/kg), pyresis (ED_{50} = 0.3 mg/kg) and carrageenan-induced hyperalgesia (ID_{50} = 0.65 mg/kg), showing 3-6-fold higher *in vivo* efficacy than indomethacin and DuP-697.

SOURCE – Merck Frosst.

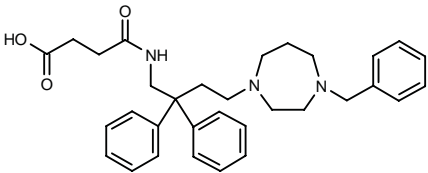
REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) 2,3,5-Trisubst. pyridines as inhibitors of cyclooxygenase-2. WO 9914194.

2. Dubé, D. et al. 2-Heterosubstituted-3-(4-methylsulfonyl)phenyl-5-trifluoromethyl pyridines as selective and orally active cyclooxygenase-2 inhibitors. Bioorg Med Chem Lett 1999, 9(12): 1715.

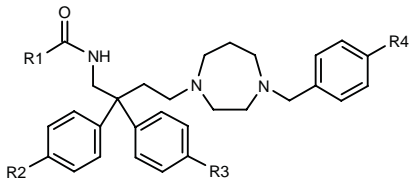
277599

N-[4-(4-Benzylperhydro-1,4-diazepin-1-yl)-2,2-diphenyl-butyl]succinamic acid

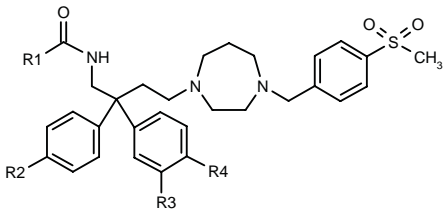


C32 H39 N3 O3; Mol wt: 513.6781

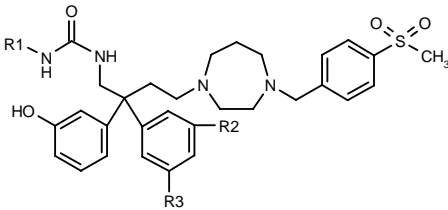
ACTION – Chemokine receptor antagonist that inhibits the action of chemokines such as macrophage inflammatory protein-1α (MIP-1α) and monocyte chemotactic protein-1 (MCP-1) on target cells, with potential in the treatment of rheumatoid arthritis, atherosclerosis, psoriasis, asthma, ulcerative colitis, glomerulonephritis, multiple sclerosis, pulmonary fibrosis and myocarditis. Other compounds from this series of cyclic diamine derivatives include the following:



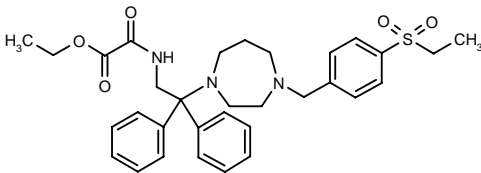
Compound	R1	R2=R3	R4	Formula
277600	2-oxo-1-pyrrolidinyl-(CH2)3NH	H	OMe	C ₃₇ H ₄₉ N ₅ O ₃
277601	1-(MeOCOCH2CH2CO)-4-Pip	H	Cl	C ₃₉ H ₄₉ ClN ₄ O ₄
277602	4-Pip-NH	H	SO2Et	C ₃₆ H ₄₉ N ₅ O ₃ S
277612	4-(PhCH2)-1-Piz	CF3	Cl	C ₄₃ H ₄₈ ClF ₆ N ₅ O
277613	NH(CH2)3OH	OH	Cl	C ₃₂ H ₄₁ ClN ₄ O ₄



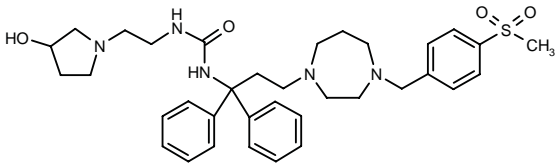
Compound	R1	R2	R3	R4	Formula
277605	CH2CO2H	H	F	H	C ₃₂ H ₃₈ FN ₃ O ₅ S
277606	H	Ph	H	Ph	C ₄₂ H ₄₅ N ₃ O ₃ S
277607	H	N(Me)2	H	N(Me)2	C ₃₄ H ₄₇ N ₅ O ₃ S
277608	Me	H	H	CO2H	C ₃₂ H ₃₉ N ₃ O ₅ S



Compound	R1	R2	R3	Formula
277609	(CH2)3OH	CF3	H	C ₃₄ H ₄₃ F ₃ N ₄ O ₅ S
277610	4-Pip	OMe	OMe	C ₃₇ H ₅₁ N ₅ O ₆ S
277611	(CH2)3OH	OH	H	C ₃₃ H ₄₄ N ₄ O ₆ S



277603: C32 H39 N3 O5 S



277604: C35 H47 N5 O4 S

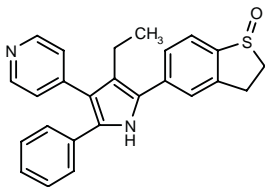
SOURCE – Teijin.

REFERENCES

1. Shioda, T. and Endo, N. (Teijin Ltd.) Phenylalkyl cyclic diamine derivs. and their medicinal use. JP 99130757.

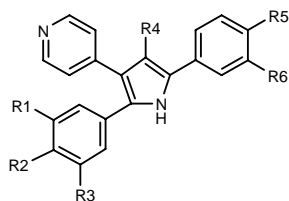
277650

5-[3-Ethyl-5-phenyl-4-(4-pyridinyl)-1H-pyrrol-2-yl]-2,3-dihydro-1-benzothiophene S-oxide

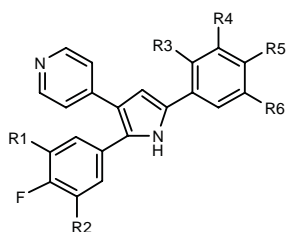


C25 H22 N2 O S; Mol wt: 398.5278

ACTION – An inhibitor of the production of proinflammatory cytokines reported to possess excellent inhibitory activity against TNF-α and IL-1β production *in vivo*. Other exemplified pyridylpyrrole derivatives include the following:



Compound	R1	R2	R3	R4	R5,R6	Formula
277653	H	H	H	Et	-SO(CH ₂) ₃ -	C ₂₆ H ₂₄ N ₂ OS
277654	F	F	H	H	-SO ₂ CH ₂ CH ₂ C(Me) ₂ -	C ₂₆ H ₂₂ F ₂ N ₂ O ₂ S
277656	H	H	H	Pr	-SOCH ₂ CH ₂ CO-	C ₂₇ H ₂₄ N ₂ O ₂ S
277659	F	F	F	H	-SO ₂ CH ₂ CH(Et)O-	C ₂₅ H ₁₉ F ₃ N ₂ O ₃ S
277660	H	H	H	H	-SOCH ₂ CH ₂ N(i-Pr)-	C ₂₆ H ₂₅ N ₃ OS
277661	Cl	H	H	H	-SOCH ₂ CH ₂ N(SO ₂ Me)-	C ₂₄ H ₂₀ ClN ₃ O ₃ S ₂
277662	Cl	F	H	H	-SO ₂ CH ₂ CH ₂ N(Bu)-	C ₂₇ H ₂₅ ClF ₃ N ₃ O ₂ S
277663	F	F	H	H	-SO(CH ₂) ₄ -	C ₂₅ H ₂₀ F ₂ N ₂ OS



Compound	R1	R2	R3	R4	R5,R6	Formula
277651	F	F	H	F	-SO ₂ CH ₂ CH ₂ -	C ₂₃ H ₁₄ F ₄ N ₂ O ₂ S
277657	H	H	H	OMe	-SO ₂ CH ₂ CH ₂ CO-	C ₂₅ H ₁₉ F ₃ N ₂ O ₄ S
277658	H	H	F	OCHF ₂	-SOCH ₂ CH ₂ O-	C ₂₄ H ₁₅ F ₄ N ₂ O ₃ S

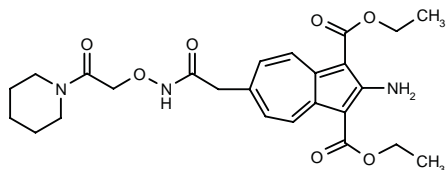
SOURCE – Sankyo.

REFERENCES

1. Kimura, T. et al. (Sankyo Co., Ltd.) *Pyridylpyrrole derivs.* JP 99209377, WO 9925717.

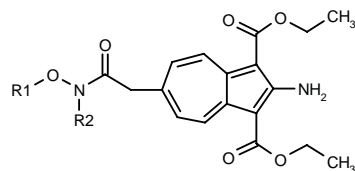
277670

2-Amino-6-[N-[2-oxo-2-(1-piperidinyl)ethoxy]carbamoylmethyl]azulene-1,3-dicarboxylic acid diethyl ester



C₂₅ H₃₁ N₃ O₇; Mol wt: 485.5339

ACTION – Orally active metalloprotease, including matrix metalloproteinase, inhibitor, a representative compound from a series of azulene derivatives, wherein the following are also included:



Compound	R1	R2	Formula
277671	CH ₂ CON(CH ₂ CH ₂ OMe) ₂	H	C ₂₆ H ₃₅ N ₃ O ₉
277672	2,2-(Me) ₂ -1,3-dioxolan-4-yl-CH ₂	H	C ₂₄ H ₃₀ N ₂ O ₈
277673	CON(Me) ₂	H	C ₂₁ H ₂₅ N ₃ O ₇
277674	1-pyrrolidinyl-COCH ₂	Me	C ₂₅ H ₃₁ N ₃ O ₇

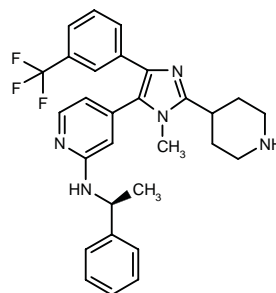
SOURCE – Roche Diagnostics.

REFERENCES

1. Friebe, W.-G. et al. (Roche Diagnostics GmbH) *Azulene derivs. and pharmaceutical compsns. containing them.* EP 922702, WO 9931078.

277685

4-[1-Methyl-2-(4-piperidinyl)-4-[3-(trifluoromethyl)phenyl]-1H-imidazol-5-yl]-N-[1(S)-phenylethyl]pyridine-2-amine



C₂₉ H₃₀ F₃ N₅; Mol wt: 505.5850

ACTION – Potent and selective inhibitor of p38 mitogen-activated protein (MAP) kinase (IC₅₀ = 0.19 nM) with greater than 4000-fold selectivity over both c-Raf and JNK2α1 kinases. Compound inhibited lipopolysaccharide (LPS)-induced TNF-α release both *in vitro* (IC₅₀ = 2.8 nM in human whole blood) and *in vivo* (ED₅₀ = 0.06 and 0.6 mg/kg i.v. and p.o., respectively, in a murine LPS challenge model). Oral bioavailability in rats and monkeys was about 85%. When given orally for 21 days, it was effective in the rat adjuvant-induced arthritis test, producing dose-dependent inhibition of secondary paw swelling with ED₅₀ values of 8.2 mg/kg (prophylactic regimen from day 1-21) and 17.5 mg/kg/day (therapeutic regimen from day 14-21). In this model, compound was also able to prevent the joint destruction in both primary and secondary paws. Potentially useful for the treatment of inflammatory diseases related to high levels of TNF-α such as rheumatoid arthritis and Crohn's disease.

SOURCE – Merck & Co.

REFERENCES

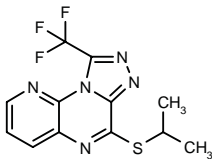
1. Selnick, H.G. et al. (Merck & Co., Inc.) *Subst. imidazoles having anti-cancer and cytokine inhibitory activity.* US 5717100, WO 9712876.

2. Liverton, N.J. et al. *Design and synthesis of potent, selective, and orally bioavailable tetrasubstituted imidazole inhibitors of p38 mitogen-activated protein kinase.* J Med Chem 1999, 42(12): 2180.

277711

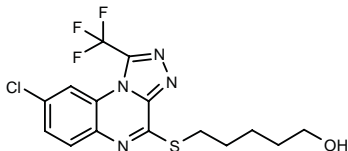
6-(Isopropylsulfanyl)-9-(trifluoromethyl)pyrido[3,2-*e*]-[1,2,4]triazolo[4,3-*a*]pyrazine

(Isopropyl)[9-(trifluoromethyl)pyrido[3,2-*e*][1,2,4]triazolo-4,3-*a*]pyrazin-6-yl] sulfide



C12 H10 F3 N5 S; Mol wt: 313.3060

ACTION – An inhibitor of adhesion molecule expression shown to inhibit E-selectin, VCAM-1 and ICAM-1 expression in stimulated human umbilical vein endothelial cells (HUVEC) with respective IC₅₀ values of 0.103, 0.032 and 0.073 μM. Potentially useful in the treatment and/or prevention of inflammatory disorders including rheumatoid arthritis, allergies, bronchial asthma, atopic dermatitis, psoriasis, ischemia–reperfusion injury, nephritis, hepatitis, multiple sclerosis, ulcerative colitis, acute respiratory distress syndrome, graft rejection, sepsis, diabetes and autoimmune diseases, as well as cancer metastasis, arteriosclerosis and AIDS. Another fused pyrazine compound is:



277713: C15 H14 Cl F3 N4 O S

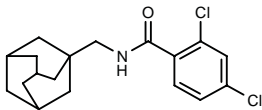
SOURCE – Ono.

REFERENCES

1. Kobayashi, K. et al. (Ono Pharmaceutical Co., Ltd.) *Fused pyrazine cpds.* WO 9924434.

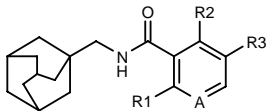
277769

N-(Adamantan-1-ylmethyl)-2,4-dichlorobenzamide



C18 H21 Cl2 N O; Mol wt: 338.2759

ACTION – P2X₇ (formerly P2Z) receptor antagonist (pIC₅₀ = 4.50 in a functional assay using the P2X₇ agonist bbATP) potentially useful in the treatment of inflammatory, immune or cardiovascular disorders and specifically claimed for effecting immunosuppression in the treatment of rheumatoid arthritis. Other representative compounds from this series of adamantane derivatives include the following:



Compound	R1	R2	R3	A	Formula
277770	OMe	OMe	H	CH	C ₂₀ H ₂₇ NO ₃
277771	H	H	Cl	CH	C ₁₈ H ₂₂ ClNO
277772	SO2Me	H	H	N	C ₁₈ H ₂₄ N ₂ O ₃ S
277773	4-MeO-PhS	H	H	N	C ₂₄ H ₂₈ N ₂ O ₂ S
277774	O(CH2)3CO2H	H	H	CH	C ₂₂ H ₂₉ NO ₄
277775	Cl	H	OCH2CH2-N(Me)2	CH	C ₂₂ H ₃₁ ClN ₂ O ₂
277776	Cl	H	1-Pip-CH2-CH2NH	CH	C ₂₅ H ₃₆ ClN ₃ O
277777	Cl	H	I	CH	C ₁₈ H ₂₁ ClINO

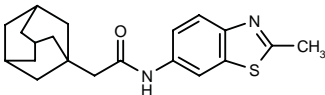
SOURCE – AstraZeneca.

REFERENCES

1. Baxter, A. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Adamantane derivs.* WO 9929661.

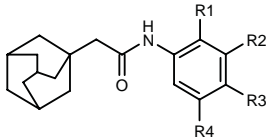
277779

2-(Adamantan-1-yl)-N-(2-methylbenzothiazol-6-yl)-acetamide



C20 H24 N2 O S; Mol wt: 340.4886

ACTION – P2X₇ (formerly P2Z) receptor antagonist (pIC₅₀ = 4.50 in a functional assay using the P2X₇ agonist bbATP) potentially useful in the treatment of inflammatory, immune or cardiovascular disorders and specifically claimed for effecting immunosuppression in the treatment of rheumatoid arthritis. Other representative compounds from this series of adamantane derivatives include the following:



Compound	R1	R2	R3	R4	Formula
277780	H	-CH=NNH-		H	C ₁₉ H ₂₃ N ₃ O
277782	Me	H	OMe	H	C ₂₀ H ₂₇ NO ₂
277785	Me	1-pyrrolidinyl-CH2CH2O	H	H	C ₂₅ H ₃₆ N ₂ O ₂
277787	Me	H	H	O(CH2)3NH2	C ₂₂ H ₃₂ N ₂ O ₂
277788	H	OMe	H	OMe	C ₂₀ H ₂₇ NO ₃
277789	Me	OH	H	OH	C ₁₉ H ₂₅ NO ₃

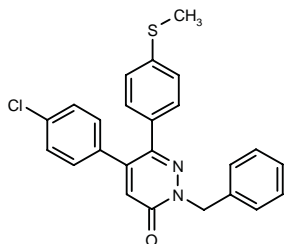
SOURCE – AstraZeneca.

REFERENCES

1. Baxter, A. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Adamantane derivs.* WO 9929660.

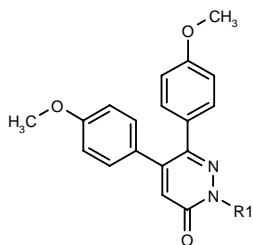
277829

2-Benzyl-5-(4-chlorophenyl)-6-[4-(methylsulfanyl)phenyl]-pyridazin-3(2*H*)-one



C₂₄ H₁₉ Cl N₂ O S; Mol wt: 418.9461

ACTION – Potent inhibitor of TNF- α and IL-6 production proven effective against collagen-induced arthritis in mice at oral doses of 1 and 3 mg/kg. No toxicity was seen in rats at 100 mg/kg/day p.o. or dogs at 30 mg/kg/day p.o. Other exemplified pyridazine derivatives include the following:



Compound	R1	Formula
277830	(E)-4-Cl-PhCH=CH	C ₂₆ H ₂₁ ClN ₂ O ₃
277831	4-MeO-PhCH ₂	C ₂₆ H ₂₄ N ₂ O ₄
277832	(CH ₂) ₃ Ph	C ₂₇ H ₂₆ N ₂ O ₃
277833	(E)-2,4-(F)2-PhCH=CH	C ₂₆ H ₂₀ F ₂ N ₂ O ₃
277834	cyclopentyl-CH ₂	C ₂₄ H ₂₆ N ₂ O ₃
277835	Et	C ₂₀ H ₂₀ N ₂ O ₃

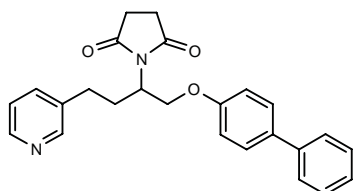
SOURCE – Kowa.

REFERENCES

1. Ohkuchi, M. et al. (Kowa Co., Ltd.) *Novel pyridazine derivs. and drugs containing the same as the active ingredient*. JP 99152274, WO 9925697.

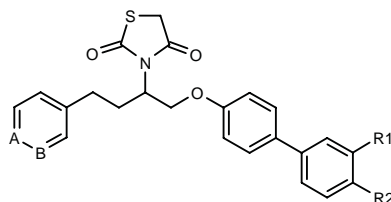
277887

(±)-1-[1-(Biphenyl-4-yloxymethyl)-3-(pyridin-3-yl)propyl]-pyrrolidine-2,5-dione

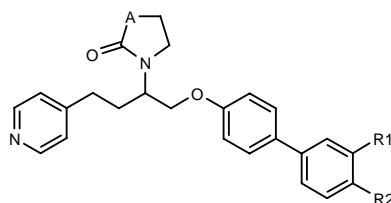


C₂₅ H₂₄ N₂ O₃; Mol wt: 400.4756

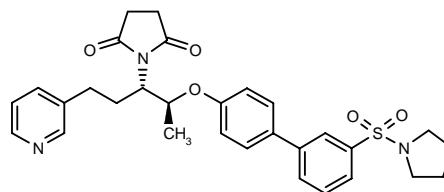
ACTION – Agent for the treatment of inflammatory, immune and cardiovascular disorders that acts as an antagonist of P2X₇ receptors (previously known as P2Z receptors), which are ligand-gated ion channels present in a variety of cells involved in the inflammatory/immune process, particularly macrophages, mast cells and lymphocytes. Other specifically claimed compounds include the following:



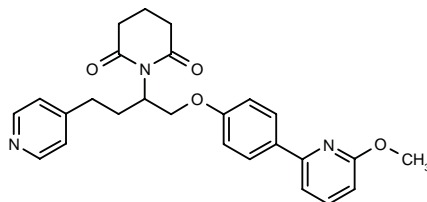
Compound	R1	R2	A	B	Isomer	Formula
277888	CN	H	CH	N	R	C ₂₅ H ₂₁ N ₃ O ₃ S
277890	NO ₂	H	N	CH	racemic	C ₂₄ H ₂₁ N ₃ O ₅ S
277891	Cl	F	CH	N	R	C ₂₄ H ₂₀ ClFN ₂ O ₃ S
277893	NH ₂	H	N	CH	S	C ₂₄ H ₂₃ N ₃ O ₃ S



Compound	R1	R2	A	Formula
277896	H	Cl	O	C ₂₄ H ₂₃ ClN ₂ O ₃
277898	NO ₂	H	CH ₂	C ₂₆ H ₂₅ N ₃ O ₄



277895: C₃₀ H₃₃ N₃ O₅ S



277897: C₂₆ H₂₇ N₃ O₄

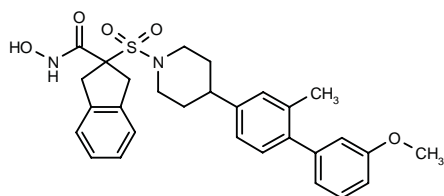
SOURCE – AstraZeneca.

REFERENCES

1. Baxter, A. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds*. WO 9929686.

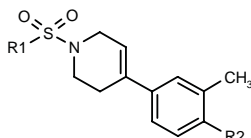
277941

2-[4-[2-Methyl-3'-(methoxy)biphenyl-4-yl]piperidin-1-yl-sulfonyl]indane-2-carboxohydroxamic acid

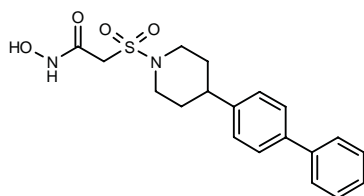


C29 H32 N2 O5 S; Mol wt: 520.6468

ACTION – Matrix metalloproteinase (MMP) inhibitor that acts as a potent inhibitor of MMP-3 (stromelysin; IC_{50} = 23 nM) and shows selectivity over other MMPs such as MMP-2 (gelatinase A; IC_{50} = 1907 nM). Potentially useful for treating or preventing rheumatoid arthritis, osteoarthritis, tissue ulceration, skin disorders, cancer metastasis, tumor angiogenesis, age-related macular degeneration and fibrotic diseases, as well as for wound repair. Other exemplified hydroxamic acid derivatives are:



Compound	R1	R2	Formula
277942	CH ₂ CONHOH	Ph	C ₂₀ H ₂₂ N ₂ O ₄ S
277948	C(allyl)(Me)CONHOH	Ph	C ₂₄ H ₂₈ N ₂ O ₄ S
277949	4-(CONHOH)-4-THP	3-EtO-Ph	C ₂₆ H ₃₂ N ₂ O ₆ S
277950	C(Me) ₂ CONHOH	3-quinolinyl	C ₂₅ H ₂₇ N ₃ O ₄ S
277951	CH ₂ CONHOH	1,3-benzodioxol-5-yl	C ₂₁ H ₂₂ N ₂ O ₆ S



277947: C19 H22 N2 O4 S

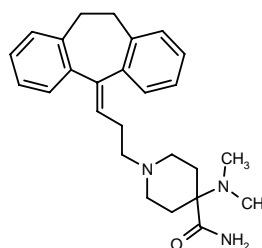
SOURCE – Pfizer.

REFERENCES

1. Dack, K.N. and Whitlock, G.A. (Pfizer Ltd.;Pfizer Inc.) *Hydroxamic acid derivs. as matrix metalloprotease (MMP) inhibitors*. WO 9929667.

278036

1-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-4-(dimethylamino)piperidine-4-carboxamide



C26 H33 N3 O; Mol wt: 403.5667

ACTION – Agent for the treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibers play a role such as neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis that acts by inhibiting the release of neuropeptides from peripheral and central endings of sensory C-fibers. Compound also inhibits the release of insulin-antagonizing peptides such as CGRP and amylin from peripheral nerve endings and is thus expected to be useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) and age-associated obesity. A specifically claimed compound from a series of tricyclic derivatives.

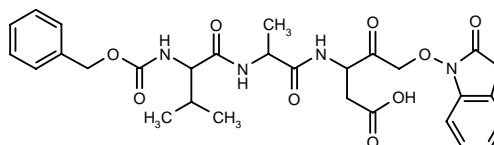
SOURCE – Novo Nordisk.

REFERENCES

1. Joergensen, T.K. et al. (Novo Nordisk A/S) *Novel heterocyclic cpds*. WO 9931058.

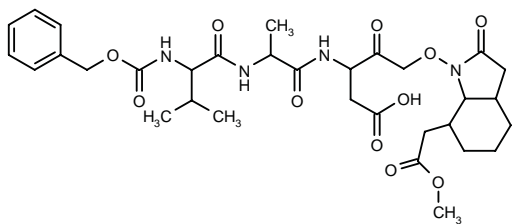
278164

3-[2-(2-Benzoyloxycarbonylamino-3-methylbutyr-amido)propionamido]-4-oxo-5-(2-oxo-2,3-dihydro-1H-indol-1-yloxy)pentanoic acid



C29 H34 N4 O9; Mol wt: 582.6066

ACTION – Agent for the treatment of stroke, reperfusion injury, Alzheimer's disease, inflammatory disorders such as arthritis and inflammatory bowel disease, septic shock and shigellosis, an inhibitor of IL-1 β -converting enzyme (ICE or caspase-1; K_i = 0.002 nM; IC_{50} = 0.003 μ M) and of other cysteine proteases from the ICE family such as Ich-2 (caspase-4; IC_{50} = 0.005 μ M). Compound was also shown to inhibit IL-1 β production in human peripheral blood mononuclear cells (PBMCs; IC_{50} = 3.0 μ M). Another compound from this series of specifically claimed hydroxamate derivatives is:



278165: C32 H44 N4 O11

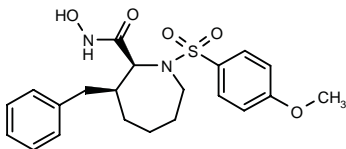
SOURCES – BASF; Warner-Lambert.

REFERENCES

1. Allen, H.J. et al. (Warner-Lambert Co.;BASF AG) *Hydroxamate inhibitors of interleukin-1β converting enzyme*. US 5919790.

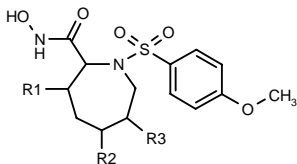
278233

cis-3-Benzyl-1-(4-methoxyphenylsulfonyl)hexahydro-1*H*-azepine-2-carboxydroxamic acid



C21 H26 N2 O5 S; Mol wt: 418.5114

ACTION – Agent for the treatment of inflammation, tissue degradation and related disorders, an inhibitor of matrix metalloproteinases such as human neutrophil collagenase and human fibroblast stromelysin, as well as of the production of TNF-α. Within this series of specifically claimed azepine derivatives, the following are also included:



Compound	R1	R2	R3	Isomer	Formula
278234	H	H	H		C ₁₄ H ₂₀ N ₂ O ₅ S
278235	CH ₂ CO ₂ Me	bond			C ₁₇ H ₂₂ N ₂ O ₇ S
278236	CONH(CH ₂) ₃ Ph	H	H		C ₂₄ H ₃₁ N ₃ O ₆ S
278237	4-Ph-PhCH ₂	H	H	trans	C ₂₇ H ₃₀ N ₂ O ₅ S
278238	NHCO ₂ CH ₂ Ph	bond			C ₂₂ H ₂₅ N ₃ O ₇ S

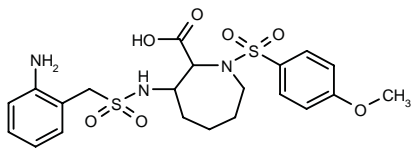
SOURCE – Amgen.

REFERENCES

1. Russo-Rodriguez, S.E. et al. (Amgen Inc.) *Azepine or larger medium ring derivs. and their use as pharmaceuticals*. WO 9932451.

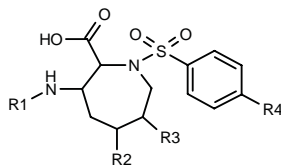
278239

3-(2-Aminobenzylsulfonamido)-1-(4-methoxyphenylsulfonyl)hexahydro-1*H*-azepine-2-carboxylic acid



C21 H27 N3 O7 S2; Mol wt: 497.5903

ACTION – Matrix metalloproteinase inhibitor useful in the treatment of inflammation, tissue degradation and related disorders. It inhibits human fibroblast stromelysin and/or human neutrophil collagenase and is therefore preferably of use in the prophylaxis and treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, peridontitis, gingivitis, corneal, epidermal and gastric ulceration, tumor metastasis, invasion and growth, neuroinflammatory disorders (e.g., multiple sclerosis) and angiogenesis-dependent diseases. Other specifically claimed carboxylic acid substituted heterocycles are:



Compound	R1	R2	R3	R4	Formula
278240	SO ₂ CH ₂ Ph	H	H	OMe	C ₂₁ H ₂₆ N ₂ O ₇ S ₂
278241	SO ₂ CH ₂ Ph	bond		4-Cl-Ph	C ₂₆ H ₂₅ ClN ₂ O ₆ S ₂
278242	2-NO ₂ -PhCH ₂ SO ₂	bond		OMe	C ₂₁ H ₂₃ N ₃ O ₉ S ₂
278243	4-Cl-PhCH ₂ OCO	bond		OMe	C ₂₂ H ₂₃ ClN ₂ O ₇ S
278253	3,5-(Cl) ₂ -PhCH ₂ OCO	bond		OMe	C ₂₂ H ₂₂ Cl ₂ N ₂ O ₇ S

SOURCE – Amgen.

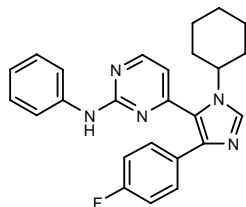
REFERENCES

1. Koch, K. et al. (Amgen Inc.) *Carboxyl acid substd. heterocycles as metalloproteinase inhibitors*. WO 9932452.

278322

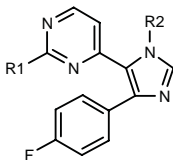
4-[1-Cyclohexyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl]-*N*-phenylpyrimidin-2-amine

N-[4-[1-Cyclohexyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl]pyrimidin-2-yl]aniline



C25 H24 F N5; Mol wt: 413.4976

ACTION – Inhibitor of the production of cytokines including IL-1, IL-8 and TNF that acts by inhibiting the MAP kinase p38/CSBP/RK kinase. Potentially useful in the treatment of cytokine-mediated disorders such as arthritic conditions, sepsis, septic shock, Alzheimer’s disease, stroke, restenosis, reperfusion injury, asthma, adult respiratory distress syndrome, osteoporosis, graft-vs.-host reaction, transplant rejection, inflammatory bowel disease, ulcerative colitis, multiple sclerosis, eczema, psoriasis and conjunctivitis, particularly inflammation and osteoporosis. Other specifically claimed 1,4,5-substituted imidazoles include the following:



Compound	R1	R2	Formula
278323	4-imidazolyl-CH2CH2NH	cyclohexyl	C ₂₄ H ₂₆ FN ₇
278324	NHCH(Me)CH2CH2Ph	cyclohexyl	C ₂₉ H ₃₂ FN ₅
278325	3,4-(Cl)2-PhCH2	3,4-(MeO)2-Ph-CONHCH2CH2	C ₃₁ H ₂₆ Cl ₂ FN ₅ O ₃
278326	NHPh	i-Pr	C ₂₂ H ₂₀ FN ₅
278327	2-Me-5-F-PhNH	4-Pip	C ₂₅ H ₂₄ F ₂ N ₆
278328	NHPh	4-F-Ph	C ₂₅ H ₁₇ F ₂ N ₅

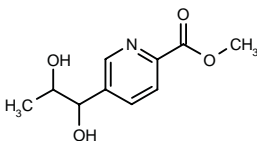
SOURCE – SmithKline Beecham.

REFERENCES

1. Gallagher, T.F. et al. (SmithKline Beecham Corp.) *Cpds. of heteroaryl substid. imidazole, their pharmaceutical compsns. and uses.* WO 9932121.

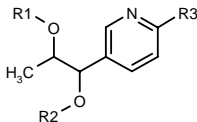
278329

5-(1,2-Dihydroxypropyl)pyridine-2-carboxylic acid methyl ester



C10 H13 N O4; Mol wt: 211.2157

ACTION – Antiinflammatory agent isolated from a culture of a fungus *Marasmiellus* sp. (FERM BP-5735) with IL-1 and TNF production-inhibitory activity. Other compounds isolated from this source include the following:



Compound	R1	R2	R3	Formula
278330	H	Ac	CO2Me	C ₁₂ H ₁₅ NO ₅
278331	H	H	CO2H	C ₉ H ₁₁ NO ₄
278332	Ac	Ac	CO2Me	C ₁₄ H ₁₇ NO ₆
278333	4-Br-PhCO	4-Br-PhCO	CO2Me	C ₂₄ H ₁₉ Br ₂ NO ₆

Compound	R1	R2	R3	Formula
278334	H	H	CONH2	C ₉ H ₁₂ N ₂ O ₃
278335	H	H	CON(Me)2	C ₁₁ H ₁₆ N ₂ O ₃
278336	H	H	CN	C ₉ H ₁₀ N ₂ O ₂
278337	H	H	2-Me-5-tetrazolyl	C ₁₀ H ₁₃ N ₅ O ₂
278338	H	H	1-Me-5-tetrazolyl	C ₁₀ H ₁₃ N ₅ O ₂

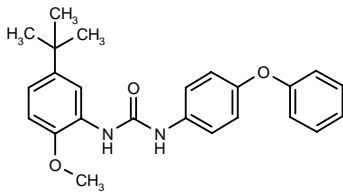
SOURCE – Pfizer.

REFERENCES

1. Hirai, H. et al. (Pfizer Inc.) *Picolin acid derivs. useful in the treatment of IL-1 and TNF mediated diseases.* CA 2253080, EP 926137, JP 99222480.

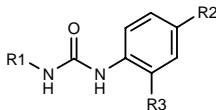
278372

N-(5-tert-Butyl-2-methoxyphenyl)-N’-[4-(phenoxy)-phenyl]urea



C24 H26 N2 O3; Mol wt: 390.4804

ACTION – p38 MAP kinase inhibitor that inhibits the production of cytokines such as TNF-α, IL-1 and IL-8, and matrix metalloproteinases such as MMP-1 (collagenase) and MMP-3 (stromelysin). Potentially useful in the treatment of osteoarthritis, rheumatoid arthritis, osteoporosis, asthma, septic shock, inflammatory bowel disease or graft-versus-host reaction. Other representative compounds from this series of symmetrical and unsymmetrical diphenyl ureas are:



Compound	R1	R2	R3	Formula
278373	2-MeO-5-CF3-Ph	Me	H	C ₁₆ H ₁₅ F ₃ N ₂ O ₂
278374	2-MeO-5-(SO2CHF2)-Ph	Me	H	C ₁₆ H ₁₆ F ₂ N ₂ O ₄ S
278375	3-MeO-2-Naph	H	F	C ₁₈ H ₁₅ FN ₂ O ₂

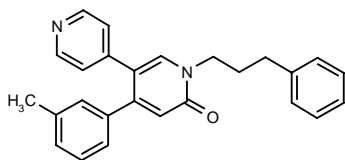
SOURCE – Bayer.

REFERENCES

1. Miller, S. et al. (Bayer Corp.) *Inhibition of p38 kinase using symmetrical and unsymmetrical diphenyl ureas.* WO 9932463.

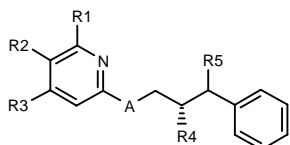
278406

4-(3-Methylphenyl)-1-(3-phenylpropyl)-5-(pyridin-4-yl)-pyridin-2(1*H*)-one

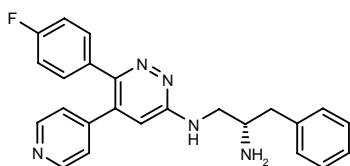


C₂₆ H₂₄ N₂ O; Mol wt: 380.4886

ACTION – Cytokine inhibitor useful for the treatment of disorders mediated by TNF- α , IL-1 β , IL-6 and/or IL-8, particularly inflammation, but also pain, cancer and diabetes. It exhibited IC₅₀ values of 20 μ M or less for inhibition of lipopolysaccharide (LPS)-stimulated TNF release in monocytes. Other specifically claimed substituted pyridine and pyridazine compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
278408	H	4-Pyr	3-Me-Ph	NH ₂	H	O	C ₂₆ H ₂₅ N ₃ O
278409	H	3-CF ₃ -Ph	4-Pyr	H	NH ₂	NH	C ₂₆ H ₂₃ F ₃ N ₄
278410	H	4-Cl-Ph	4-Pyr	NH ₂	H	NH	C ₂₆ H ₂₃ ClN ₄
278412	4-Pyr	4-MeO-Ph	H	NH ₂	H	NH	C ₂₆ H ₂₆ N ₄ O
278413	4-Pyr	3-Me-Ph	H	NH ₂	H	NH	C ₂₆ H ₂₆ N ₄



278411: C₂₄ H₂₂ F N₅

The compounds of the invention also inhibit Raf kinase and may therefore be useful in the treatment of cancer.

SOURCE – Amgen.

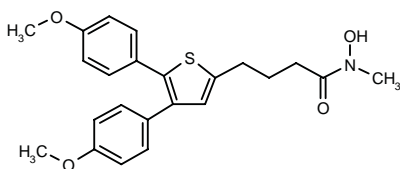
REFERENCES

1. Mantlo, N.B. et al. (Amgen Inc.) *Substd. pyridine and pyridazine cpds. and their pharmaceutical use*. WO 9932448.

S-19812*

242289

4-[4,5-Bis(4-methoxyphenyl)thien-2-yl]-*N*-hydroxy-*N*-methylbutyramide



C₂₃ H₂₅ N O₄ S; Mol wt: 411.5240

ACTION – Antiinflammatory agent, a dual cyclooxygenase and lipoxygenase inhibitor proven to reduce both paw swelling and bone loss (48 and 35% inhibition, respectively, at 10 mg/kg/day p.o. for 28 days.) in rats with adjuvant-induced arthritis and to reduce both the incidence (56.7% reduction at 40 mg/kg/day p.o.) and the severity of collagen-induced arthritis in mice (62% reduction at 40 mg/kg/day p.o. for 5 days). Compound showed excellent gastric tolerability: it did not induce gastric erosions at up to 800 mg/kg p.o. in fasted mice and rats and it did not modify basal gastric acid secretion *in vivo* or *in vitro*.

SOURCE – Servier.

REFERENCES

1. Wierzbicki, M. et al. (ADIR et Cie.) *Thiophene cpds., process for their preparation and pharmaceutical compsns. containing them*. EP 728755, FR 2730996, JP 96253470.

2. Pastoureaux, P. et al. *Activity of S 19812, a dual inhibitor of cyclooxygenase and lipoxygenase pathways, in rodents with chronic arthritis*. Mediators Inflamm 1999, 8(Suppl. 1): Abst P-14-10.

3. Tordjman, C. et al. *Gastric tolerability of S 19812, a dual inhibitor of cyclooxygenase and lipoxygenase pathways*. Mediators Inflamm 1999, 8(Suppl. 1), Abst P-14-8.

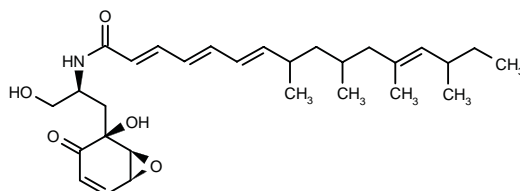
*Identified compound **242289** (see **241831**) Drug Data Report 1997, 019(01): 0077.

SCYPHOSTATIN

277750

(2*E*,4*E*,6*E*,12*E*)-*N*-[2-Hydroxy-1(*S*)-[1(*S*)-hydroxy-5(*S*),6(*S*)-epoxy-2-oxocyclohex-3-en-1-ylmethyl]ethyl]-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide

F-10463A



C₂₉ H₄₃ N O₅; Mol wt: 485.6607

Pale yellow powder, [α]_D²⁵ +66.4° (c 0.09, MeOH).

ACTION – Neutral sphingomyelinase (N-SMase) inhibitor extracted from the culture broth of *Trichopeziza mollissima*, giving an IC₅₀ of 1.0 μ M for the inhibition of rat brain microsome N-SMase and exhibiting comparable potency against N-SMase from human myeloid leukemia U937, human leukemia Molt-4, murine fibrosarcoma L929 and human T-cell leukemia Jurkat cells; it was approximately 50-fold less potent in inhibiting lysosomal acidic SMase (IC₅₀ = 49.3 μ M) and inactive against bacterial N-SMases, phosphatidylcholine-specific phospholipase C, phosphatidic acid-specific phosphohydrolase, cathepsin L and IL-1 β -converting enzyme. In human peripheral blood monocytes compound inhibited the lipopolysaccharide (LPS)-induced production of IL-1 β (IC₅₀ = 0.1 μ M) and was approximately 10-fold less potent in inhibiting other inflammatory mediators such as PGE₂, IL-6, IL-8 and TNF- α (IC₅₀ = 0.8, 1.4, 2.1 and 1.3 μ M, respectively). Compound (25-100 mg/kg p.o.) showed antiinflammatory activity against carrageenan-induced paw edema in rats and was devoid of toxic effects at up to 300 mg/kg p.o. in mice.

SOURCE – Sankyo.

REFERENCES

1. Ogita, T. et al. (Sankyo Co., Ltd.) *Novel cpd. F-10463a*. JP 95233158, WO 9518119.

2. Masahiro, T. et al. *Structural elucidation of scyphostatin, an inhibitor of membrane-bound neutral sphingomyelinase*. J Am Chem Soc 1997, 119(33): 7871.

3. Nara, F. et al. *Biological activities of scyphostatin, a neutral sphingomyelinase inhibitor from a discomycete, Trichopeziza mollissima*. J Antibiot 1999, 52(6): 531.

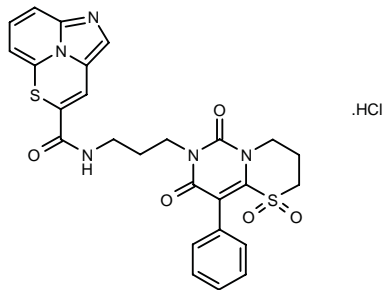
4. Nara, F. et al. *Scyphostatin, a neutral sphingomyelinase inhibitor from dyscomycete, Trichopeziza mollissima: Taxonomy of the producing organism, fermentation, isolation, and physico-chemical properties*. J Antibiot 1999, 52(6): 525.

5. Tanaka, M. et al. *Isolation and structural elucidation of scyphostatin, an inhibitor of neutral sphingomyelinase*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1997, 39241.

IMMUNOMODULATING AGENTS

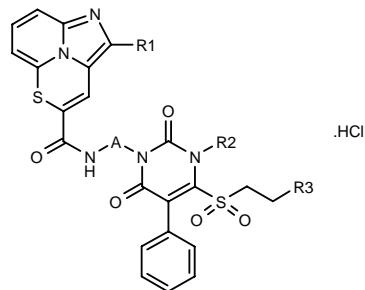
277825

N-[3-(9-Phenyl-1,1,6,8-tetraoxo-2,3,4,6,7,8-hexahydropyrimido[6,1-b][1,3]thiazin-7-yl)propyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide hydrochloride



C26 H23 N5 O5 S2 . HCl; Mol wt: 586.0906

ACTION – Potent cell adhesion molecule expression inhibitor proven to inhibit ICAM-1 and ELAM-1 expression in TNF-α-stimulated human umbilical vein endothelial cells (HUVEC) with respective IC₅₀ values of 1.71 and 0.69 μM. At doses of 3 and 10 mg/kg/day i.p., it delayed rejection in a murine skin allotransplantation model from 12.6-14.9 days in controls to 19.4 and 22.8 days, respectively. This compound also improved diabetic nephropathy in KKA^y mice at a dose of 50 mg/kg/day p.o. for 3 weeks. Other compounds from this series of tricyclic imidazole derivatives include the following:



Compound	R1	R2	R3	A	Formula
277826	Me	-CH2-	-(CH2)3-		C ₂₇ H ₂₅ N ₅ O ₅ S ₂ .HCl
277827	H	CH2Ph	H	-(CH2)4-	C ₃₃ H ₃₁ N ₅ O ₅ S ₂ .HCl
277828	H	Me	H	-(CH2)4-	C ₂₇ H ₂₇ N ₅ O ₅ S ₂ .HCl

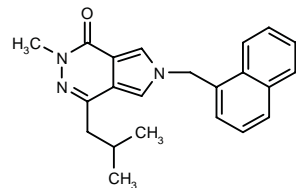
SOURCE – Takeda.

REFERENCES

1. Abe, H. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic imidazole derivs., their preparation method and agents*. JP 99130778.

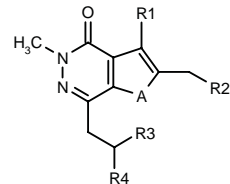
277857

4-Isobutyl-2-methyl-6-(1-naphthylmethyl)-2,6-dihydro-1 H-pyrrolo[3,4-*d*]pyridazin-1-one

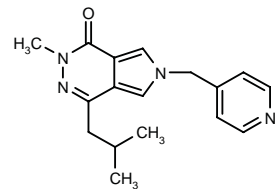


C22 H23 N3 O; Mol wt: 345.4437

ACTION – Immunosuppressant proven to inhibit lymphocyte proliferation in a human mixed lymphocyte reaction (MLR) test with an IC₅₀ value < 1 μM. Potentially useful for the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases, as well as immunologically mediated diseases including transplant rejection and AIDS, and also reported to be useful as an antimicrobial agent. Within this series of specifically claimed pyrrolo-, thieno-, furano- and pyrazolo[3,4-*d*]pyridazinones, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
277858	S(CH2)3OH	1-Naph	Me	Me	S	C ₂₅ H ₂₈ N ₂ O ₂ S ₂
277861	H	3-CN-Ph	Me	Me	O	C ₁₉ H ₁₉ N ₃ O ₂
277863	OCH2CH2-C(Me)2OH	3-CF3-Ph	-CH2CH2-		S	C ₂₄ H ₂₇ F ₃ N ₂ O ₃ S



277860: C17 H20 N4 O

SOURCE – AstraZeneca.

REFERENCES

1. Bantick, J. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds*. WO 9929695.

SOURCE – Sankyo.

REFERENCES

1. Ogita, T. et al. (Sankyo Co., Ltd.) *Novel cpd. F-10463a*. JP 95233158, WO 9518119.

2. Masahiro, T. et al. *Structural elucidation of scyphostatin, an inhibitor of membrane-bound neutral sphingomyelinase*. J Am Chem Soc 1997, 119(33): 7871.

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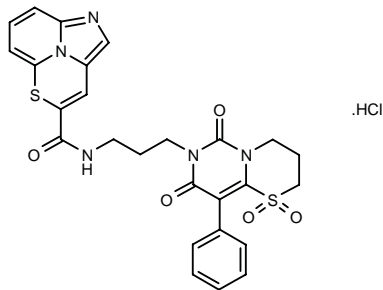
4. Nara, F. et al. *Scyphostatin, a neutral sphingomyelinase inhibitor from dyscomycete, Trichopeziza mollissima: Taxonomy of the producing organism, fermentation, isolation, and physico-chemical properties*. J Antibiot 1999, 52(6): 525.

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IMMUNOMODULATING AGENTS

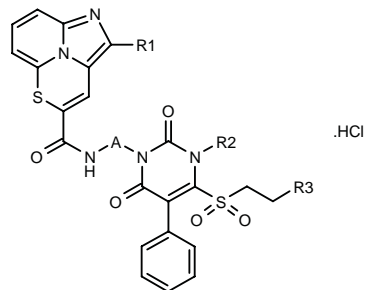
277825

N-[3-(9-Phenyl-1,1,6,8-tetraoxo-2,3,4,6,7,8-hexahydropyrimido[6,1-b][1,3]thiazin-7-yl)propyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide hydrochloride



C26 H23 N5 O5 S2 . HCl; Mol wt: 586.0906

ACTION – Potent cell adhesion molecule expression inhibitor proven to inhibit ICAM-1 and ELAM-1 expression in TNF-α-stimulated human umbilical vein endothelial cells (HUVEC) with respective IC₅₀ values of 1.71 and 0.69 μM. At doses of 3 and 10 mg/kg/day i.p., it delayed rejection in a murine skin allotransplantation model from 12.6-14.9 days in controls to 19.4 and 22.8 days, respectively. This compound also improved diabetic nephropathy in KKA^y mice at a dose of 50 mg/kg/day p.o. for 3 weeks. Other compounds from this series of tricyclic imidazole derivatives include the following:



Compound	R1	R2	R3	A	Formula
277826	Me	-CH2-	-(CH2)3-		C ₂₇ H ₂₅ N ₅ O ₅ S ₂ .HCl
277827	H	CH2Ph	H	-(CH2)4-	C ₃₃ H ₃₁ N ₅ O ₅ S ₂ .HCl
277828	H	Me	H	-(CH2)4-	C ₂₇ H ₂₇ N ₅ O ₅ S ₂ .HCl

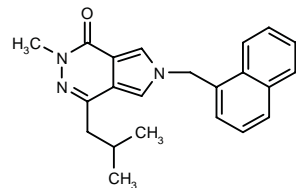
SOURCE – Takeda.

REFERENCES

1. Abe, H. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic imidazole derivs., their preparation method and agents*. JP 99130778.

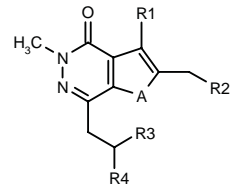
277857

4-Isobutyl-2-methyl-6-(1-naphthylmethyl)-2,6-dihydro-1 H-pyrrolo[3,4-d]pyridazin-1-one

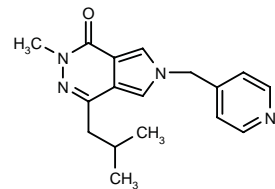


C22 H23 N3 O; Mol wt: 345.4437

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Compound	R1	R2	R3	R4	A	Formula
277858	S(CH2)3OH	1-Naph	Me	Me	S	C ₂₅ H ₂₈ N ₂ O ₂ S ₂
277861	H	3-CN-Ph	Me	Me	O	C ₁₉ H ₁₉ N ₃ O ₂
277863	OCH2CH2-C(Me)2OH	3-CF3-Ph	-CH2CH2-		S	C ₂₄ H ₂₇ F ₃ N ₂ O ₃ S



277860: C17 H20 N4 O

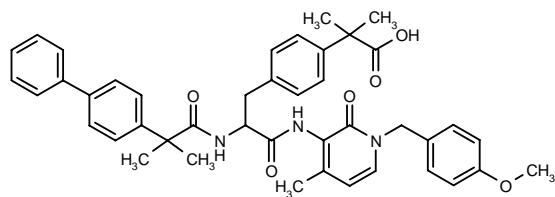
SOURCE – AstraZeneca.

REFERENCES

1. Bantick, J. et al. (Astra Pharmaceuticals Ltd.;Astra AB) *Novel cpds*. WO 9929695.

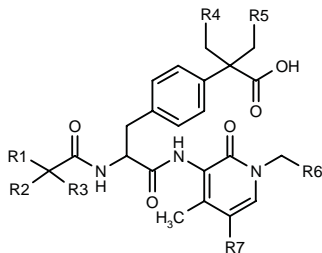
277957

2-[4-[2-[2-(4-Biphenyl)-2-methylpropionamido]-2-[N-[1-(4-methoxybenzyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]carbamoyl]ethyl]phenyl]-2-methylpropionic acid



C43 H45 N3 O6; Mol wt: 699.8435

ACTION – Immunosuppressive agent that binds to Src family SH₂ domains of particular regulatory proteins, and in particular tyrosine kinases having one or more SH₂ domains, thus disrupting the interaction of these regulatory proteins and their native ligands. *In vitro*, compound was shown to inhibit IL-2 production in human blood CD4+ T-lymphocytes after T-cell receptor and CD28 crosslinking (IC₅₀ = 25 μM). Potentially useful for the treatment of cancer, as well as autoimmune and chronic inflammatory diseases. A representative compound from a series of pyridone derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
277959	Et	2-Naph	Et	H	H	4-MeO-Ph	H	C ₄₃ H ₄₇ N ₃ O ₆
277960	Et	2-Naph	Et	-(CH2)2-		4-MeO-Ph	H	C ₄₅ H ₄₉ N ₃ O ₆
277961	H	1-Naph	Et	H	H	4-MeO-Ph	H	C ₄₁ H ₄₃ N ₃ O ₆
277962	H	2-Naph	H	H	H	4-EtO-Ph	H	C ₄₀ H ₄₁ N ₃ O ₆
277963	Me	1-Naph	Me	H	H	cyclohexyl	H	C ₄₀ H ₄₇ N ₃ O ₅
277964	Me	2-Naph	Me	H	H	1-Ph-cyclopropyl	H	C ₄₃ H ₄₅ N ₃ O ₅
277965	H	2-Naph	H	H	H	4-MeO-Ph	Br	C ₃₉ H ₃₈ BrN ₃ O ₆

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Betageri, R. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Pyridones as SRC family SH2 domain inhibitors*. WO 9931066.

Hu5C8

259623

Anti-CD154 humanized monoclonal antibody

5c8
Anti-CD40 ligand MAb
Antova™

ACTION – Humanized monoclonal antibody to CD154 (also known as CD40L or CD40 Ligand, and 5c8 antigen) that is able to block the CD40/CD154 pathway and thereby to prevent allograft rejection and graft-versus-host disease, to alter the course of autoimmunity and to prevent the production of proinflammatory mediators by activated macrophages and endothelial cells. Compound prevents islet allograft rejection in rhesus monkeys and baboons, inducing long-term survival without inhibiting islet cell function and with no evidence of toxicity or infectious complications. The MAb was seen to prevent acute renal allograft rejection in rhesus monkeys for a mean of 220 days after termination of therapy.

SOURCE – Biogen.

REFERENCES

1. Kirk, A.D. et al. (Biogen, Inc.) *Use of a CD40:CD154 binding interruptor to prevent counter adaptive immune responses, particularly graft rejection*. WO 9852606.

2. Thomas, D.W. (Biogen, Inc.) *C154 blockade therapy for autoimmune diseases*. WO 9900143.

3. Baumgartner, R.E. et al. *Rhesus renal allografts contain non-destructive activated lymphocytic infiltrates following anti-CD154 therapy*. Transplantation 1999, 67(7): Abst 226.

4. Blair, P.J. et al. *Colocation of CD40L (CD154) and CD3 results in CD4 T cell activation and the induction of apoptosis*. Transplantation 1999, 67(7): Abst 500.

5. George, J. et al. *Safety and effect on platelet count of single-dose monoclonal antibody to CD40 ligand (ANTOVA™) in patients with chronic ITP*. Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2906.

6. Gobburu, J.V.S. et al. *Pharmacokinetics/dynamics of 5c8, a monoclonal antibody to CD154 (CD40 ligand) suppression of an immune response in monkeys*. J Pharmacol Exp Ther 1998, 286(2): 925.

7. Gobburu, J.V.S. et al. *Pharmacokinetics/pharmacodynamics of 5c8, a monoclonal antibody to CD154 (CD40 ligand): Suppression of an immune response in monkeys*. Pharm Res 1997, 14(11, Suppl.): Abst 1258.

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11. Kenyon, N.S. et al. *Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154*. Proc Natl Acad Sci USA 1999, 96(14): 8132.

12. Kirk, A. et al. *Long-term rejection-free survival in primate allotransplantation with costimulation blockade*. Transplantation 1999, 67(7): Abst 2.

13. Kirk, A.D. et al. *Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates*. Nat Med 1999, 5(6): 686.

14. Minozzo, M. et al. *Blockade of signals one and two using anti-CD45RB and anti-CD40L allows induction of tolerance in islet allotransplantation*. 9th Cong Eur Soc Organ Transplant (June 19-24, Oslo) 1999, Abst 203.

15. Minozzo, M. et al. *Successful discordant human xenotransplantation following interference with signals one and two using anti-CD45RB and anti-CD40L*. 9th Cong Eur Soc Organ Transplant (June 19-24, Oslo) 1999, Abst 89.

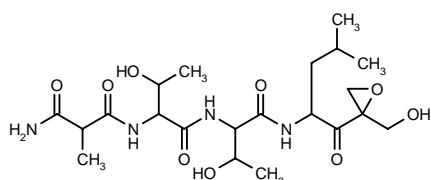
16. *Biogen: Q3 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, Oct 21.

17. Biogen, Inc. Annual Report 1997.

SPA-1761B

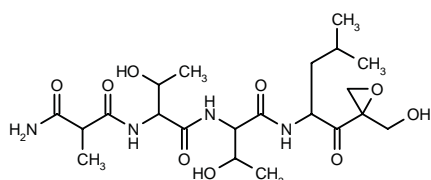
278069

N^1 -[2-Hydroxy-1-[N -[2-hydroxy-1-[N -[1-[2-(hydroxymethyl)oxiran-2-ylcarbonyl]-3-methylbutyl]carbamoyl]-propyl]carbamoyl]propyl]-2-methylpropanediamide isomer B



C21 H36 N4 O9; Mol wt: 488.5344

ACTION – Proteasome inhibitor isolated from a culture of *Streptomyces* sp. SPA-1761 (FERM P-16341), shown to be more potent than the known compound SPA-1344*, as demonstrated by IC_{50} values of 0.22 and 0.45 μ g/ml, respectively, against enzyme from rat brain tissue. Potentially useful for the treatment of autoimmune diseases. Another compound isolated from the same source is:



SPA-1761A [278070]: C21 H36 N4 O9: isomer A

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Kojima, S. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Proteasome inhibitors*. JP 99124397.

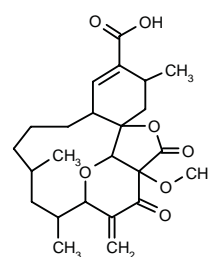
*See **Eponemycin** Drug Data Rep 1989, 011(10): 0872.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

277803

3-Methoxy-6,8,14-trimethyl-16-methylene-2,17-dioxo-3,3a,5,6,7,8,9,10,11,11a,14,15-dodecahydro-3,5-ethano-2*H*-furo[2,3-*o*][2]benzoxacycloundecin-13-carboxylic acid



C24 H32 O7; Mol wt: 432.5098

ACTION – Antineoplastic and antibacterial agent, a chrolactomycin compound obtained by culturing the microorganism *Streptomyces* sp. 569N-3 (FERM BP-6158); it gave MIC values of 5.2-10.4 μ g/ml against *Staphylococcus aureus* ATCC 6538P, *Enterococcus hirae* ATCC10541 and *Bacillus subtilis* No. 10707, and IC_{50} values of 0.45-1.6 μ M against human breast cancer MCF-7, human bladder cancer T24, human epidermoid cancer A431 and human renal cancer ACHN cells.

SOURCE – Kyowa Hakko.

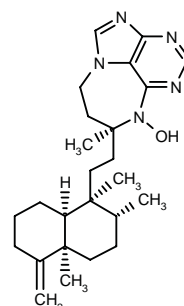
REFERENCES

1. Yamashita, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Chrolactomycin cpd*. CA 2256252, EP 924212, JP 99180984.

ASMARINE B

278475

9(*S*)-Methyl-9-[2-[(1*S*,2*R*,4*aR*,8*aS*)-5-methylene-1,2,4a-trimethylperhydronaphthalen-1-yl]ethyl]-7,8,9,10-tetrahydro[1,4]diazepino[1,2,3-*gh*]purin-10-ol



C25 H37 N5 O; Mol wt: 423.6013

15. Minozzo, M. et al. *Successful discordant human xenotransplantation following interference with signals one and two using anti-CD45RB and anti-CD40L*. 9th Cong Eur Soc Organ Transplant (June 19-24, Oslo) 1999, Abstr 89.

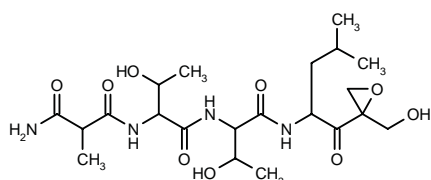
16. *Biogen: Q3 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, Oct 21.

17. Biogen, Inc. Annual Report 1997.

SPA-1761B

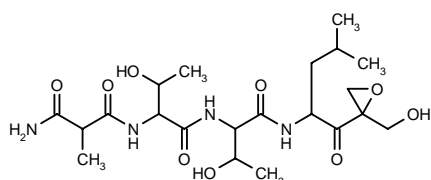
278069

N^1 -[2-Hydroxy-1-[N -[2-hydroxy-1-[N -[1-[2-(hydroxymethyl)oxiran-2-ylcarbonyl]-3-methylbutyl]carbamoyl]-propyl]carbamoyl]propyl]-2-methylpropanediamide isomer B



C₂₁ H₃₆ N₄ O₉; Mol wt: 488.5344

ACTION – Proteasome inhibitor isolated from a culture of *Streptomyces* sp. SPA-1761 (FERM P-16341), shown to be more potent than the known compound SPA-1344*, as demonstrated by IC₅₀ values of 0.22 and 0.45 µg/ml, respectively, against enzyme from rat brain tissue. Potentially useful for the treatment of autoimmune diseases. Another compound isolated from the same source is:



SPA-1761A [278070]: C₂₁ H₃₆ N₄ O₉: isomer A

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Kojima, S. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Proteasome inhibitors*. JP 99124397.

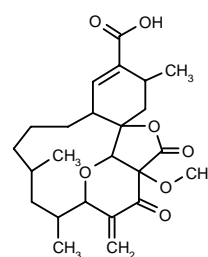
*See **Eponemycin** Drug Data Rep 1989, 011(10): 0872.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

277803

3-Methoxy-6,8,14-trimethyl-16-methylene-2,17-dioxo-3,3a,5,6,7,8,9,10,11,11a,14,15-dodecahydro-3,5-ethano-2*H*-furo[2,3-*o*][2]benzoxacycloundecin-13-carboxylic acid



C₂₄ H₃₂ O₇; Mol wt: 432.5098

ACTION – Antineoplastic and antibacterial agent, a chrolactomycin compound obtained by culturing the microorganism *Streptomyces* sp. 569N-3 (FERM BP-6158); it gave MIC values of 5.2-10.4 µg/ml against *Staphylococcus aureus* ATCC 6538P, *Enterococcus hirae* ATCC10541 and *Bacillus subtilis* No. 10707, and IC₅₀ values of 0.45-1.6 µM against human breast cancer MCF-7, human bladder cancer T24, human epidermoid cancer A431 and human renal cancer ACHN cells.

SOURCE – Kyowa Hakko.

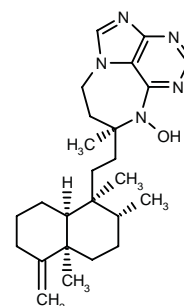
REFERENCES

1. Yamashita, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Chrolactomycin cpd*. CA 2256252, EP 924212, JP 99180984.

ASMARINE B

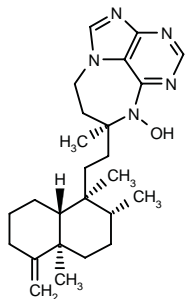
278475

9(*S*)-Methyl-9-[2-[(1*S*,2*R*,4*aR*,8*aS*)-5-methylene-1,2,4a-trimethylperhydronaphthalen-1-yl]ethyl]-7,8,9,10-tetrahydro[1,4]diazepino[1,2,3-*gh*]purin-10-ol



C₂₅ H₃₇ N₅ O; Mol wt: 423.6013

ACTION – Cytotoxic diterpene alkaloid isolated from the sponge *Raspailia* sp., active against murine leukemia P388, human lung carcinoma A-549, human colon carcinoma HT-29 and human melanoma MEL-28 tumor cell lines, with IC₅₀ values of 0.12-0.24 μM. Another compound isolated from the same sponge is:



Asmarine A [278476]: C₂₅ H₃₇ N₅ O

SOURCE – Instituto Biomar.

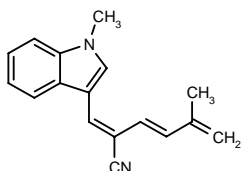
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1. Rudi, A. et al. (Instituto Biomar SA) *Cytotoxic alkaloid derivs. including asmarine A and B isolated from a sponge*. WO 9933832.

0089-D

278473

5-Methyl-2-[(*E*)-1-methyl-1*H*-indol-3-ylmethylene]hexa-3(*E*),5-dienitrile



C₁₇ H₁₆ N₂; Mol wt: 248.3274

ACTION – Alkaloid-type compound isolated from *Nocardia brasiliensis* IFM 0089 (FERM BP-5542) with strong cytotoxicity against murine leukemia L1210 and P388, doxorubicin-resistant P388 and human epidermoid carcinoma KB cells (IC₅₀ = 0.25-0.75 μg/ml), as well as a broad spectrum of antimicrobial activity against bacteria such as *Micrococcus luteus* IFM2066, *Bacillus subtilis* PCI189, *Mycobacterium smegmatis* ATCC607 and *Aspergillus niger* ATCC40606 (MIC = 0.39-3.13 μg/ml).

SOURCE – Higeta Shoyu.

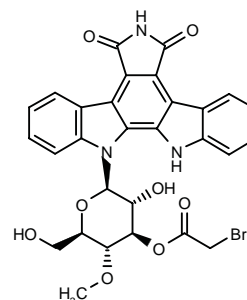
REFERENCES

1. Nemoto, A. et al. (Higeta Shoyu Co., Ltd.) *Indole alkaloid type cpd. 0089-D*. US 5922582.

DNA-INTERCALATING DRUGS

277054

12-[3-*O*-(Bromoacetyl)-4-*O*-methyl-β-D-glucopyranosyl]-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione



C₂₉ H₂₄ Br N₃ O₈; Mol wt: 622.4256

Yellow solid.

ACTION – Antineoplastic agent, a rebeccamycin analogue that inhibits topoisomerase I (MIC = 1.61 μM against calf thymus topo I) and exerts cytotoxic activity against both camptothecin-sensitive and camptothecin-resistant P388 leukemia cells (IC₅₀ = 0.16 and 3.2 μM, respectively). Compound also showed good anti-HIV-1 activity but high cytotoxicity in HIV-1_{Lai}-infected CEM-SS cells (IC₅₀ = 0.15 μM; CC₅₀ = 0.44 μM), giving a low selectivity index (SI = 2.9). Some antimicrobial activity was noted against *Bacillus cereus* (MIC = 5.02 μM), but it was inactive against both *Escherichia coli* and *Candida albicans*.

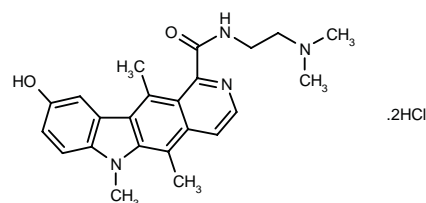
SOURCES – Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR); INSERM (FR); Université Louis Pasteur, Strasbourg (FR); Novartis; Rhône-Poluenc Rorer.

REFERENCES

1. Moreau, P. et al. *Syntheses and biological activities of rebeccamycin analogues. Introduction of a halogenoacetyl substituent*. J Med Chem 1999, 42(4): 584.

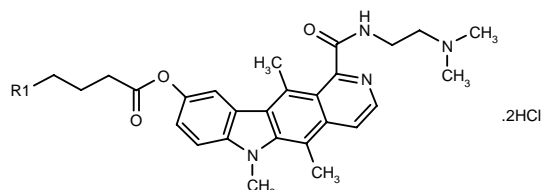
277698

N-[2-(Dimethylamino)ethyl]-9-hydroxy-5,6,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide dihydrochloride



C₂₃ H₂₆ N₄ O₂ · 2HCl; Mol wt: 463.4062

ACTION – Antineoplastic agent with *in vitro* cytotoxicity against murine leukemia L1210 and melanoma B16 cells (IC_{50} = 13.4 and 3.4 nM, respectively). Compound induced an accumulation of L1210 cells in the G2/M phase of the cell cycle, reflecting inhibition of DNA topoisomerase II activity. In mice bearing leukemia P388, compound (40 mg/kg i.v. on day 1) induced > 80% long-term survivors, with a TC% > 600; it was also highly active when given at a dose of 10 mg/kg i.v. on days 1, 5 and 9 (TC% > 600). Other related ellipticine analogues include the following:



Compound	R1	Formula
277717	CH ₂ CO ₂ H	C ₂₉ H ₃₄ N ₄ O ₅ ·2HCl
277720	CO ₂ H	C ₂₈ H ₃₂ N ₄ O ₅ ·2HCl

SOURCE – Servier.

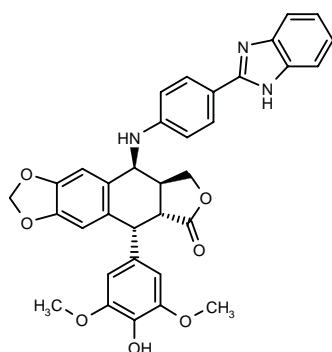
REFERENCES

1. Guillonnet, C. et al. (ADIR et Cie.) *Bis pyrido[4,3-b]carbazole cpds., process for their preparation and pharmaceutical compns. containing them*. CA 2244508, EP 895995, FR 2767132, JP 99100379.

2. Guillonnet, C. et al. *Synthesis of 9-O-substituted derivatives of 9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (2-(dimethylamino)ethyl)amide and their 10- and 11-methyl analogues with improved antitumor activity*. J Med Chem 1999, 42(12): 2191.

277846

(5*R*,5*aR*,8*aS*,9*S*)-9-[4-(1*H*-Benzimidazol-2-yl)phenyl-amino]-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8*a*,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5*aH*)-one



C34 H29 N3 O7; Mol wt: 591.6171

M.p. 82-4 °C; $[\alpha]_D^{25}$ -75° (*c* 0.02, CHCl₃).

ACTION – Antineoplastic agent, a DNA topoisomerase II inhibitor (IC_{100} = 10 μM), being almost 10-fold more potent than etoposide (IC_{100} = 100 μM). Compound was active *in vitro* against a panel of human tumor cell lines, showing significant inhibitory effect against epidermoid nasopharyngeal carcinoma KB, lung carcinoma A549, ileocecal carcinoma HCT-8, renal carcinoma CAKI-1, breast adenocarcinoma MCF-7 and melanoma SKMEL-2 (ED_{50} = 0.20, 0.23, 0.63, 0.35, 0.85 and 0.45 μM, respectively) and against drug-resistant KB subclones such as etoposide- and vincristine-resistant cells (ED_{50} = 0.45 and 1.40 μM, respectively). In murine models of

antitumor activity, compound was significantly less effective than etoposide against etoposide-sensitive leukemia P388/00, and inactive against etoposide-resistant MCF-7 tumors.

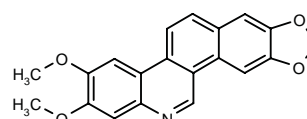
SOURCE – Genelabs.

REFERENCES

1. Zhu, X.-K. et al. *Antitumor agents. 194. Synthesis and biological evaluations of 4-beta-mono-, -di-, and -trisubstituted aniline-4'-O-demethyl-podophyllotoxin and related compounds with improved pharmacological profiles*. J Med Chem 1999, 42(13): 2441.

278043

2,3-Dimethoxy[1,3]benzodioxolo[5,6-*f*]phenanthridine



C20 H15 N O4; Mol wt: 333.3415

ACTION – Antineoplastic agent with topoisomerase I-inhibitory activity and cytotoxicity against human lymphoblast RPMI 8042 cells and the camptothecin-resistant variant CPT-K5 (IC_{50} = 7.5 and 7.0 μM, respectively).

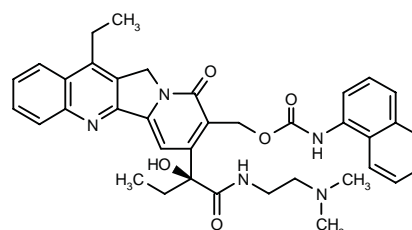
SOURCE – State University of New Jersey, Piscataway, NJ (US).

REFERENCES

1. Lavoie, E.J. et al. (State University of New Jersey) *Heterocyclic cytotoxic agents*. WO 9931067.

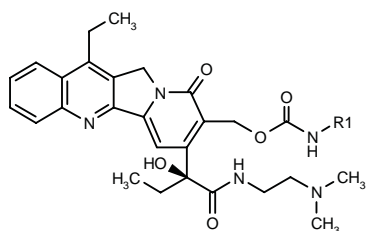
278147

N-(1-Naphthyl)carbamic acid 7-[1(*S*)-[*N*-(2-(dimethylamino)ethyl)carbamoyl]-1-hydroxypropyl]-12-ethyl-9-oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-8-ylmethyl ester



C37 H39 N5 O5; Mol wt: 633.7451

ACTION – Water-soluble camptothecin derivative with excellent antitumor activity, as demonstrated in mice bearing murine leukemia L1210 following i.p. administration of doses of 3.13-200 mg/kg on days 1, 5 and 9. Other representative compounds include the following:



Compound	R1	Formula
278148	Pr	C ₃₀ H ₃₉ N ₅ O ₅
278149	2-F-Ph	C ₃₃ H ₃₆ FN ₅ O ₅
278151	3-F-Ph	C ₃₃ H ₃₆ FN ₅ O ₅
278152	4-F-Ph	C ₃₃ H ₃₆ FN ₅ O ₅

SOURCES – Daiichi Pharmaceutical; Yakult Honsha.

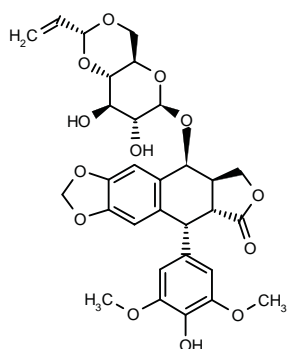
REFERENCES

1. Ogawa, T. et al. (Yakult Honsha Co., Ltd.; Daiichi Pharmaceutical Co., Ltd.) *Novel camptothecin derivs.* JP 99140085, WO 9924430.

278474

(5*R*,5*aR*,8*aR*,9*S*)-5-(3,5-Dimethoxy-4-hydroxyphenyl)-9-[4,6-*O*-(*R*)-(propenylidene)-β-D-glucopyranosyloxy]-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one

4'-Demethyl-4-*O*-[4,6-*O*-(*R*)-(propenylidene)-β-D-glucopyranosyl]epipodophyllotoxin



C30 H32 O13; Mol wt: 600.5698

ACTION – Antineoplastic agent, a representative compound from a series of 4'-*O*-demethyl-epipodophyllotoxin-β-D-glucoside acetal derivatives that displays superior antitumor activity to etoposide against human lung cancer A-549, ovarian adenocarcinoma SK-OV-3, malignant melanoma SK-MEL-2, CNS cancer XF-498 and colon cancer HCT-15 cell lines giving IC₅₀ values of 0.01-0.33 μg/ml vs. 0.69-2.52 μg/ml; it was also more potent than the reference in inhibiting topoisomerase II (IC₅₀ = 2.0 μg/ml vs. 10.0 μg/ml for etoposide). The compound was also significantly more active than etoposide in increasing survival in mice bearing murine leukemia L1210.

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

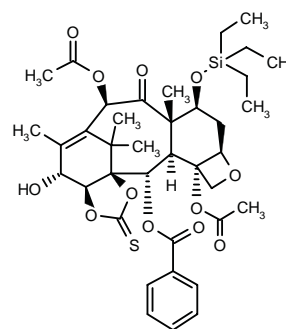
1. No, Z.S. et al. (Korea Research Institute of Chemical Technology) *4'-O-Demethyl-epipodophyllotoxin-β-D-glucoside acetal derivs.* WO 9932499.

ANTIMITOTIC DRUGS

277934

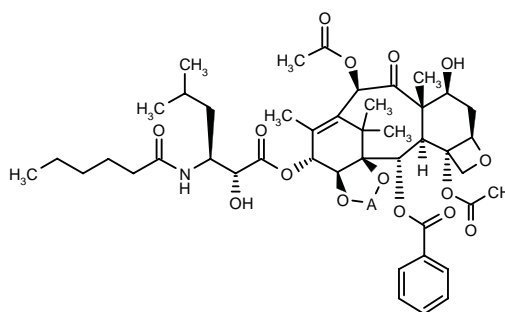
14β-Hydroxy-7-*O*-(triethylsilyl)baccatin III 1-*O*,14-*O*-cyclic thiocarbonate

(2*aR*,4*S*,4*aS*,6*R*,9*S*,10*S*,11*S*,12*S*,12*aR*,12*bS*)-6,12*b*-Diacetoxy-12-benzoyloxy-9,10,11-trihydroxy-4*a*,8,13,13-tetramethyl-4-(triethylsilyloxy)-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]-benzo[1,2-*b*]oxet-5-one 10-*O*,11-*O*-cyclic thiocarbonate



C38 H50 O12 S Si; Mol wt: 758.9530

ACTION – Antineoplastic agent suitable for preparation in both oral and injectable formulations. It showed cytotoxic IC₅₀ values against murine leukemia L1210, human ovarian cancer A121, human non-small cell lung cancer A549, human colon cancer HT-59, human breast cancer MCF-7 and doxorubicin-resistant human breast cancer MCF-7/ADR cells of 0.5, 0.8, 2.3, 0.3, 1.2 and 18 nM, respectively, versus values for paclitaxel of 7.5, 4.7, 5.7, 6.9, 4.8 and 395 nM, respectively. Other specifically claimed baccatine derivatives include the following:



Compound	A	Formula
277935	-CS-	C ₄₅ H ₅₉ NO ₁₅ S
277936	-SO-	C ₄₄ H ₅₈ NO ₁₆ S

SOURCE – Indena.

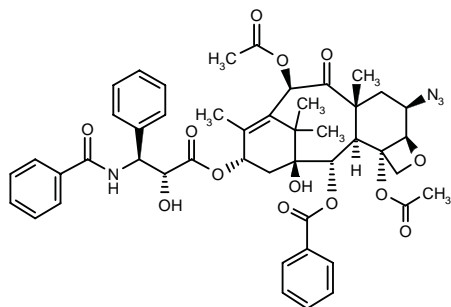
REFERENCES

1. Bombardelli, E. (Indena SpA) *10-Deacetyl-14β-hydroxybaccatine III derivs., a process for the preparation thereof and formulations containing them.* US 5917056, WO 9636622.

278283

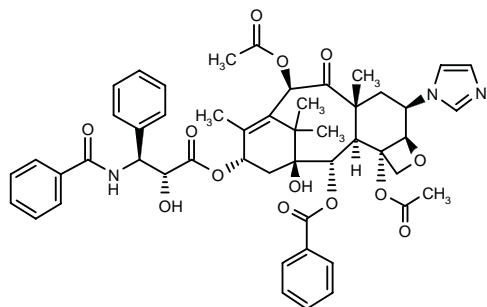
6 β -Azido-7-deoxypaclitaxel

[2a*R*,3*R*,4a*R*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12a*R*,12b*S*]-6,12b-Diacetoxy-3-azido-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz-[1,2-*b*]oxet-5-one



C47 H50 N4 O13; Mol wt: 878.9270

ACTION – Antineoplastic agent, a paclitaxel derivative giving an IC₅₀ of 0.63 nM (IC₅₀ paclitaxel = 1.53-2.73 nM) for cytotoxicity to human colon tumor HCT116 cells. Another exemplified 7-deoxy-6-nitrogen substituted paclitaxel is:



278284: C50 H53 N3 O13

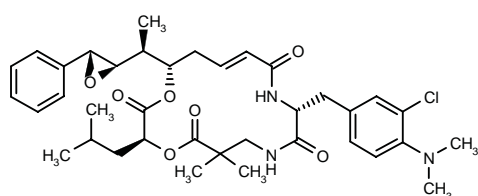
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Wittman, M.D. (Bristol-Myers Squibb Co.) 7-Deoxy-6-nitrogen subst. paclitaxels. WO 9932109.

278354

(3*S*,10*R*,16*S*)-10-[3-Chloro-4-(dimethylamino)benzyl]-16-[2(*R*),3(*R*)-epoxy-1(*R*)-methyl-3-phenylpropyl]-3-isobutyl-6,6-dimethyl-1,4-dioxo-8,11-diazacyclohexadec-13(*E*)-ene-2,5,9,12-tetraone



C37 H48 Cl N3 O7; Mol wt: 682.2532

White powder, $[\alpha]_D^{589} +27.6^\circ$ (c 0.31, CHCl₃).

ACTION – Antineoplastic agent, an analogue of cryptophycin with potent cytotoxic activity (IC₅₀ = 54 pM) in human leukemia CCRF-CEM cells.

SOURCE – Lilly.

REFERENCES

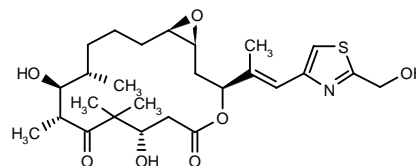
1. Patel, V.F. et al. Novel cryptophycin antitumor agents: Synthesis and cytotoxicity of fragment "B" analogues. J Med Chem 1999, 42(14): 2588.

EPOTHILONE E

277397

[1*S*,3*S*(*E*),7*S*,10*R*,11*S*,12*S*,16*R*]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[2-[2-(hydroxymethyl)-4-thiazolyl]-1-methylvinyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

[4*S*,7*R*,8*S*,9*S*,13*R*,14*S*,16*S*(*E*)]-13,14-Epoxy-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[2-[2-(hydroxymethyl)-thiazol-4-yl]-1-methylvinyl]-1-oxacyclohexadecane-2,6-dione



C26 H39 N O7 S; Mol wt: 509.6601

$[\alpha]_D^{22} -27.5^\circ$ (c 0.20, CHCl₃).

ACTION – Antineoplastic agent that exerts its potent cytotoxic activity via stabilization of microtubule assembly, a mechanism similar to that of paclitaxel. Compound is more potent than paclitaxel and retains activity against both paclitaxel-resistant and other multidrug-resistant cell lines.

SOURCES – GBF; Scripps Research Institute, La Jolla, CA (US).

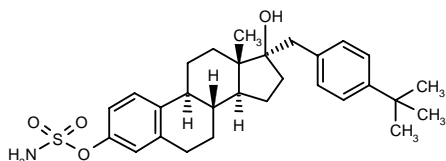
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2. Reichenbach, H. et al. (Gesellschaft für Biotechnologische Forschung mbH) Epothilone C, D, E and F, production process, and their use as cytostatic as well as phytosanitary agents. WO 9822461.
3. Finlay, R. Metathesis vs metastasis: The chemistry and biology of the epothilones. Chem Ind 1997, (24): 991.
4. Nicolaou, K.C. et al. Synthesis and biological properties of C12,13-cyclopropyl-epothilone A and related epothilones. Chem Biol 1998, 5(7): 365.
5. Nicolaou, K.C. et al. Total synthesis of epothilone E and analogs with modified side chains through the Stille coupling reaction. Angew Chem Int Ed 1998, 37(1-2): 84.
6. Nicolaou, K.C. et al. Total synthesis of epothilone E and related side-chain modified analogues via a stille coupling based strategy. Bioorg Med Chem 1999, 7(5): 665.

HORMONAL AGENTS

268002

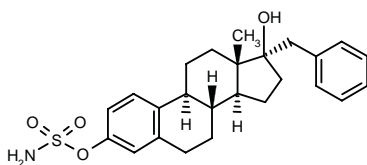
Sulfamic acid 17 α -(4-*tert*-butylbenzyl)-17-hydroxyestra-1,3,5(10)-trien-3-yl ester



C29 H39 N O4 S; Mol wt: 497.6961

White solid.

ACTION – Steroid sulfatase inhibitor able to inhibit the conversion of both dehydroepiandrosterone sulfate (DEHAS) and estrone sulfate (E_1S) to the corresponding unconjugated steroids (IC_{50} = 0.15 and 1.4 nM, respectively, in HEK293 cells transiently transfected with steroid sulfatase). Compound was 14- and 4-fold more potent than the reference compound EMATE in inhibiting DEHAS and E_1S transformation, respectively. Potentially useful for the treatment of hormone-dependent diseases such as prostate and breast cancer. Another related compound is:



268003: C25 H31 N O4 S

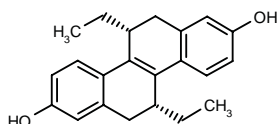
SOURCE – Laval University, Quebec (CA).

REFERENCES

1. Ciobanu, L.C. et al. *Potent inhibition of steroid-sulfatase activity by estradiol derivatives bearing two kinds of pharmacophores at positions C3 and C17 α* . 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 280.
2. Ciobanu, L.C. et al. *Potent inhibition of steroid sulfatase activity by 3-O-sulfamate 17 α -benzyl(or 4'-*tert*-butylbenzyl)estra-1,3,5(10)-trienes: Combination of two substituents at positions C3 and C17 α of estradiol*. J Med Chem 1999, 42(12): 2280.

277850

5(*R*),11(*R*)-Diethyl-5,6,11,12-tetrahydrochrysene-2,8-diol



C22 H24 O2; Mol wt: 320.4296

Off-white crystals, m.p. 241-3 °C.

ACTION – Potent and selective estrogen receptor (ER) antagonist with 6-fold selectivity for human ER β over ER α receptors and pure antagonist activity on ER β , as demonstrated in a transcriptional assay in HEC-1 cells. Potentially useful as a tool for evaluating the biological role of the ER β receptor and also for the treatment of estrogen-dependent breast cancer.

SOURCE – University of Illinois, Chicago, IL (US).

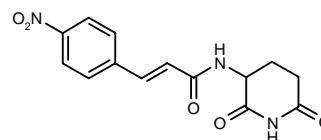
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1. Meyers, M.J. et al. *Estrogen receptor subtype-selective ligands: Asymmetric synthesis and biological evaluation of cis- and trans-5,11-dialkyl-5,6,11,12-tetrahydrochrysenes*. J Med Chem 1999, 42(13): 2456.
2. Sun, J. et al. *Novel ligands that function as selective estrogens or antiestrogens for estrogen receptor-alpha or estrogen receptor-beta*. Endocrinology 1999, 140(2): 800.

SGI-101

278347

N-(2,6-Dioxopiperidin-3-yl)-3-(4-nitrophenyl)-2-propenamide



C14 H13 N3 O5; Mol wt: 303.2727

ACTION – Antineoplastic agent, an analogue of the estrogen antagonist antineoplaston A10 with anti-proliferative activity against breast cancer MCF-7 cells.

SOURCE – Mansoura University, Mansoura (EG).

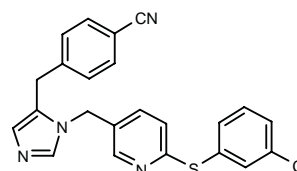
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1. Hendry, L.B. *Computer-based design and screening of molecules using DNA interactions*. US 588741.
2. Hendry, L.B. *Design of drugs involving receptor-ligand-DNA interactions*. WO 9514791.
3. El-Kerdawy, M. et al. *Computer-aided drug design of new antiestrogens*. J Antimicrob Chemother 1999, 44(Suppl. A): Abst P177.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

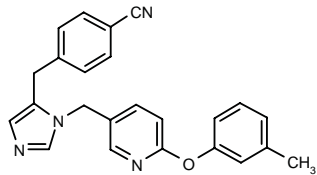
275796

4-[1-[6-(3-Chlorophenylsulfanyl)pyridin-3-ylmethyl]-1*H*-imidazol-5-ylmethyl]benzonitrile



C23 H17 Cl N4 S; Mol wt: 416.9343

ACTION – Antineoplastic agent, an inhibitor of protein prenyltransferases and the prenylation of the oncogene protein Ras. Another specifically claimed compound is:



275797: C24 H20 N4 O

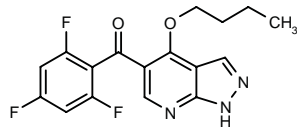
SOURCE – Merck & Co.

REFERENCES

1. Desolms, S.J. et al. (Merck & Co., Inc.) *Inhibitors of prenyl-protein transferase*. WO 9918096.

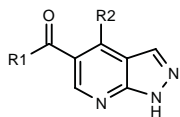
277973

1-(4-Butoxy-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1-(2,4,6-trifluorophenyl)methanone



C17 H14 F3 N3 O2; Mol wt: 349.3106

ACTION – Cyclin-dependent kinase (CDK) inhibitor with IC₅₀ values of < 50 μM against cdc2/cyclin B1, cdk2/cyclin E and cdk4/cyclin D1 kinase activity. Potentially useful for the treatment of proliferative disorders including cancer, Alzheimer’s disease, arthritis, inflammation and cardiovascular disease. Other specifically claimed pyrazolo[3,4-*b*]pyridine derivatives are:



Compound	R1	R2	Formula
277974	2,3,5,6-(F)4-4-Me-Ph	OBu	C ₁₈ H ₁₅ F ₄ N ₃ O ₂
277975	i-BuNH	OBu	C ₁₅ H ₂₂ N ₄ O ₂
277976	Ph	cyclohexyl-CH2O	C ₂₀ H ₂₁ N ₃ O ₂
277977	Ph	OCH2Ph	C ₂₀ H ₁₅ N ₃ O ₂
277978	Ph	SBu	C ₁₇ H ₁₇ N ₃ OS
277979	Ph	SOBu	C ₁₇ H ₁₇ N ₃ O ₂ S
277980	Ph	SO2Bu	C ₁₇ H ₁₇ N ₃ O ₃ S

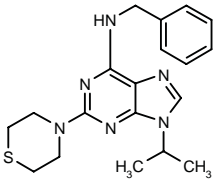
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Misra, R.N. et al. (Bristol-Myers Squibb Co.) *Use of pyrazolo[3,4-*b*]pyridine as cyclin dependent kinase inhibitors*. WO 9930710.

278249

N-Benzyl-9-isopropyl-2-(thiomorpholin-4-yl)-9*H*-purin-6-amine



C19 H24 N6 S; Mol wt: 368.5066

M.p. 137-41 °C.

ACTION – Antineoplastic agent, a cyclin-dependent kinase CDK2 inhibitor (IC₅₀ = 0.9 μM) with *in vitro* antiproliferative activity against a panel of human cell cancer lines including lung carcinoma A549 (IC₅₀ = 11 μM), ovarian carcinoma SKOV-3 (IC₅₀ = 22 μM), melanoma SKMEL-2 (IC₅₀ = 35 μM), CNS carcinoma XF-498 (IC₅₀ = 27 μM) and colon carcinoma HCT15 (IC₅₀ = 22 μM).

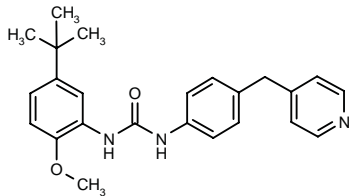
SOURCE – LG Chem.

REFERENCES

1. Oh, C.-H. et al. *Synthesis and biological activities of C-2, N-9 substituted 6-benzylaminopurine derivatives as cyclin-dependent kinase inhibitor*. Arch Pharm 1999, 332(6): 187.

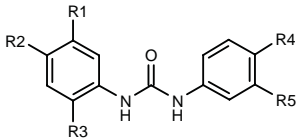
278384

N-(5-*tert*-Butyl-2-methoxyphenyl)-*N*’-[4-(pyridin-4-yl-methyl)phenyl]urea

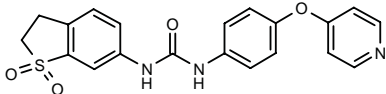


C24 H27 N3 O2; Mol wt: 389.4963

ACTION – Raf kinase inhibitor useful for treating cancer cell growth, in particular for the treatment of solid tumors. Other exemplified substituted diphenyl ureas include the following:



Compound	R1	R2	R3	R4	R5	Formula
278385	t-Bu	H	3-thienyl	4-Pyr-O	H	C ₂₆ H ₂₅ N ₃ O ₂ S
278386	t-Bu	H	H	1,3-benzo-dioxol-5-yl-O	H	C ₂₄ H ₂₄ N ₂ O ₄
278387	t-Bu	H	OMe	H	2-benzo-thiazolyl-O	C ₂₅ H ₂₅ N ₃ O ₃ S
278388	t-Bu	H	F	4-Pyr-O	H	C ₂₂ H ₂₂ FN ₃ O ₂
278389	CF ₃	Cl	H	H	2-Me-4-Pyr-O	C ₂₀ H ₁₅ ClF ₃ N ₃ O ₂
278390	NO ₂	H	OMe	4-Pyr-O	H	C ₁₉ H ₁₆ N ₄ O ₅



278391: C20 H17 N3 O4 S

SOURCE – Bayer.

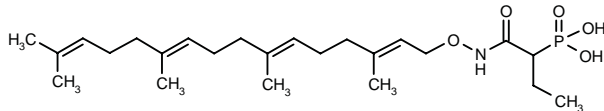
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1. Miller, S. et al. (Bayer Corp.) *Inhibition of raf using symmetrical and unsymmetrical substd. diphenyl ureas*. WO 9932436.

BAL-9602

277914

1-[N-[3,7,11,15-Tetramethyl-2(E),6(E),10(E)14-hexadeca-tetraenyloxy]carbamoyl]propylphosphonic acid



C24 H42 N O5 P; Mol wt: 455.5718

ACTION – Antineoplastic agent, a specific inhibitor of protein geranylgeranyltransferase proven to significantly inhibit the growth of human colon adenocarcinoma WiDr xenografts in nude mice following i.p. administration.

SOURCE – Baldacci.

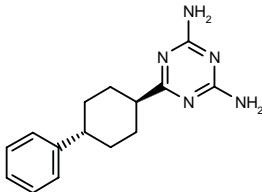
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1. Balsamo, A. et al. (Laboratori Baldacci) *Novel geranylgeranyl-derivs., process for the preparation thereof and related pharmaceutical compsns.* EP 862575, WO 9719091.
2. Danesi, R. et al. *In vivo anti-tumor activity and toxicity of novel inhibitors of protein geranylation.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PW97.

ANGIOGENESIS INHIBITORS

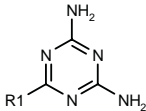
278181

trans-6-(4-Phenylcyclohexyl)-1,3,5-triazine-2,4-diamine



C15 H19 N5; Mol wt: 269.3501

ACTION – Angiogenesis inhibitor, as demonstrated *in vitro* by 100% inhibition of basic fibroblast growth factor (bFGF)-induced migration of human microvascular endothelial cells (HMVEC) at a concentration of 600 nM. Potentially useful for the treatment of angiogenic diseases, particularly cancer, diabetic retinopathy and macular degeneration. Other compounds from this series of triazine derivatives include the following:



Compound	R1	Formula
278182	4-(4-NO2-Ph)-Ph	C ₁₅ H ₁₂ N ₆ O ₂
278183	2,2-(Me)2-2H-1-benzopyran-6-yl	C ₁₄ H ₁₅ N ₅ O
278184	1,4-benzodioxan-2-yl	C ₁₁ H ₁₁ N ₅ O ₂
278185	1-adamantyl	C ₁₃ H ₁₉ N ₅
278186	4-(PhSO2)-Ph	C ₁₅ H ₁₃ N ₅ O ₂ S
278187	2-pyrazinyl	C ₇ H ₁₃ N ₇

SOURCE – Abbott.

REFERENCES

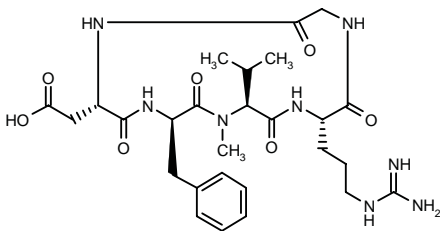
1. Henkin, J. et al. (Abbott Laboratories Inc.) *Triazine angiogenesis inhibitors*. WO 9931088.

EMD-121974*

253338

Cyclo[arginyl-glycyl-aspartyl-D-phenylalanyl-(N-methyl)-valyl]

EMD-85189



C27 H40 N8 O7; Mol wt: 588.6689

ACTION – Antiangiogenic agent, an integrin $\alpha_v\beta_3$ antagonist (IC_{50} = 4.8 nM) with high selectivity over integrin $\alpha_v\beta_5$ receptors (IC_{50} = 450 nM). Simultaneous treatment with compound and tumor-specific antibody–IL-2 fusion proteins induced dramatic primary tumor regression in three syngeneic murine tumor models of melanoma, colon carcinoma and neuroblastoma, and eradicated micrometastases. In rabbits with adjuvant-induced arthritis, compound given intraarticularly was effective in reducing arthritis severity by inhibiting synovial angiogenesis and reducing synovial cell infiltrate, pannus formation and cartilage erosions. Potentially useful for the treatment of angiogenesis-related diseases such as breast cancer and rheumatoid arthritis, and currently in phase I/II clinical trials for Kaposi’s sarcoma, brain tumors and solid tumors.

SOURCE – Merck KGaA.

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2. Jonczyk, A. et al. (Merck Patent GmbH) *Cyclic adhesion inhibitors*. DE 19534177, EP 770622, JP 97132593.

3. Dechantsreiter, M.A. et al. *N-Methylated cyclic RGD peptides as highly active and selective alphavbeta3 integrin antagonists*. J Med Chem 1999, 42(16): 3033.

4. Lode, H.N. et al. *Synergy between an antiangiogenic integrin alphav antagonist and an antibody-cytokine fusion protein eradicates spontaneous tumor metastases*. Proc Natl Acad Sci USA 1999, 96(4): 1591.

5. MacDonald, T.J. et al. *Antagonist to alphav-integrin inhibits growth of orthotopically but not heterotopically transplanted brain tumors*. Proc Amer Assoc Cancer Res 1999, 40: Abst 4096.

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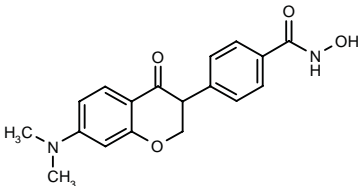
*Identified compound **253338** (see **252187**) Drug Data Report 1997, 019(09): 0806.

OTHER ONCOLYTIC DRUGS

275929

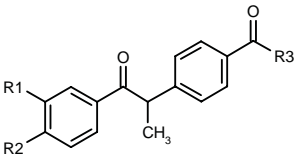
4-[7-(Dimethylamino)-4-oxo-3,4-dihydro-2H-1-benzopyran-3-yl]-N-hydroxybenzamide

4-[7-(Dimethylamino)-4-oxo-3,4-dihydro-2H-1-benzopyran-3-yl]benzohydroxamic acid



C18 H18 N2 O4; Mol wt: 326.3502

ACTION – Antineoplastic agent that is reported to selectively reverse oncogene-induced cell transformation, as demonstrated *in vitro* using NIH3T3 cells transformed with the *v-sis* gene (MIC = 0.031 μ g/ml). A representative compound from a series of 4-substituted benzoic acid derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
275930	F	1-pyrrolidinyl	OH	C ₂₀ H ₂₀ FN ₂ O ₃
275931	H	N(Me)2	NHOH	C ₁₈ H ₂₀ N ₂ O ₃
275932	H	OMe	N(Me)OH	C ₁₈ H ₁₉ NO ₄
275933	F	1-pyrrolidinyl	NHOH	C ₂₀ H ₂₁ FN ₂ O ₃

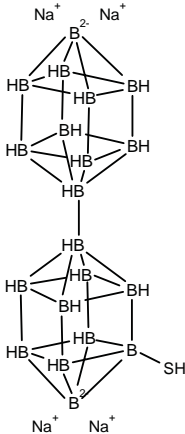
SOURCE – Shionogi.

REFERENCES

1. Haga, N. et al. (Shionogi & Co. Ltd.) *4-Substd. benzoic acid derivs. and carcinostatics containing the same as the active ingredient*. WO 9912884.

276480

1',2,3,3',4,4',5,5',6',7',7,8,8',9,9',10,10'-Heptadecahydro-6-mercapto-1,2'-bisdecaborate(4-) tetrasodium salt



H18 B20 Na4 S; Mol wt: 358.3882

ACTION – Antineoplastic agent, a boron-containing compound that, when encapsulated in tumor-selective unilamellar liposomes and administered i.v. to mice bearing mammary adenocarcinoma EMT6, was able to selectively reach the tumor mass. At low injected doses (about 10.5 mg/kg), the tumor boron concentration increased time-dependently, reaching a maximum boron concentration of 46.7 μ g/g tumor and exceeding therapeutic levels. Potentially useful for boron neutron capture therapy (BNCT) of tumors.

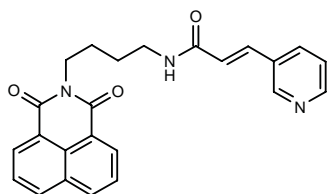
SOURCES – University of California, Los Angeles, Los Angeles, CA (US); Southwest Texas State University, San Marcos, TX (US).

REFERENCES

1. Feakes, D.A. et al. *Synthesis and in vivo murine evaluation of Na4[1-(1'-B10H9)-6-SHB10H8] as a potential agent for boron neutron capture therapy*. Proc Natl Acad Sci USA 1999, 96(11): 6406.

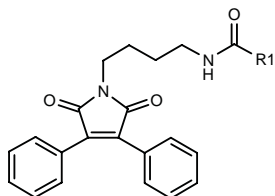
277954

N-[4-(1,3-Dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)butyl]-3-(pyridin-3-yl)-2(*E*)-propenamide



C₂₄ H₂₁ N₃ O₃; Mol wt: 399.4479

ACTION – Cytostatic and immunosuppressive agent with a broad spectrum of antiproliferative activity against human tumor cell lines, giving IC₅₀ values against human colon carcinoma HT-29, human monocytic leukemia THP-1, human lung carcinoma A549 and human hepatocellular carcinoma cells of 0.005, 0.001, 0.008 and 0.04 μM, respectively. It also showed potent immunosuppressive activity using murine spleen lymphocytes (IC₅₀ = 0.001 μM). Other representative compounds are:



Compound	R1	Formula
277955	3-Pyr-CH ₂ CH ₂	C ₂₈ H ₂₇ N ₃ O ₃
277956	(<i>E</i>)-3-Pyr-CH=CH	C ₂₈ H ₂₅ N ₃ O ₃

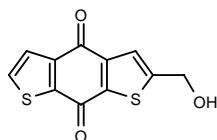
SOURCE – Klinge.

REFERENCES

1. Biedermann, E. et al. (Klinge Pharma GmbH) *Cyclic imide-substd. pyridylalkane, alkene and alkyne carboxamides useful as cytostatic and immunosuppressive agents*. DE 19756212, WO 9931087.

278090

2-(Hydroxymethyl)benzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione



C₁₁ H₆ O₃ S₂; Mol wt: 250.2974

ACTION – Antineoplastic agent with cytotoxic activity against a panel of human leukemia, small and non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer and breast cancer cell lines.

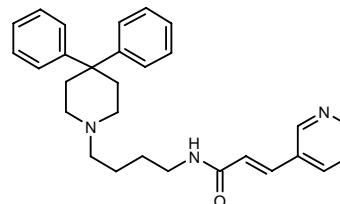
SOURCES – National Cancer Institute, Bethesda, MD (US); University of North Carolina, Chapel Hill, NC (US).

REFERENCES

1. Chao, Y.-H. et al. *Synthesis and cytotoxicity of methyl-4,8-dihydrobenzo-[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione derivatives*. Bioorg Med Chem 1999, 7(6): 1025.

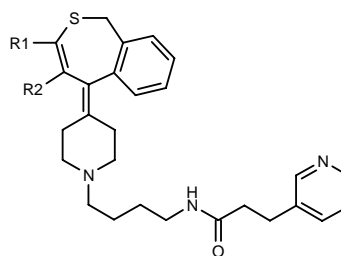
278276

N-[4-(4,4-Diphenylpiperidin-1-yl)butyl]-3-(pyridin-3-yl)-2-propenamide

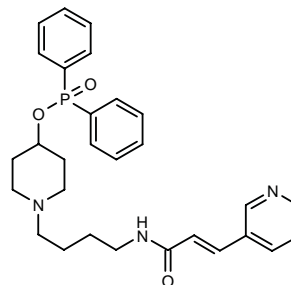


C₂₉ H₃₃ N₃ O; Mol wt: 439.5997

ACTION – Potent cytostatic and immunosuppressive agent giving IC₅₀ values of 3, 2, 0.5 and 0.3 μM, respectively, against human colon carcinoma HT-29, human lung carcinoma A549, human hepatocellular carcinoma HepG2 and human monocytic leukemia THP-1 cells. Other representative compounds from this series of piperidiny-substituted pyridylalkane, alkene and alkine carboxamides are:



Compound	R1,R2	Formula
278277	-CH=CHCH=CH-	C ₃₁ H ₃₅ N ₃ OS
278278	-SCH=CH-	C ₂₉ H ₃₃ N ₃ OS ₂



278279: C₂₉ H₃₄ N₃ O₃ P

SOURCE – Klinge.

REFERENCES

1. Biedermann, E. et al. (Klinge Pharma GmbH) *New piperidiny-substd. pyridylalkane, alkene and alkine carboxamides*. DE 19756235, WO 9931060.

PRO533

277515

Fibroblast growth factor 19

FGF-19

ACTION – Novel member of the fibroblast growth factor (FGF) family. The DNA encoding FGF-19 (PRO533) has been identified as a gene that is amplified in the genome of certain tumor cells; this amplification is expected to be associated with the overexpression of the gene product and to contribute to tumorigenesis and/or autocrine signaling. PRO533 is thus expected to be a useful target for the diagnosis and treatment of certain cancers. Methods of diagnosing and treating tumors using anti-PRO533 antibodies are described.

SOURCE – Genentech.

REFERENCES

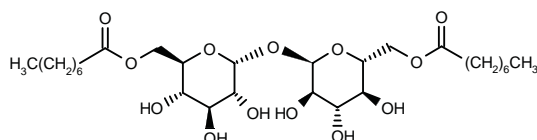
1. Botstein, D. et al. (Genentech, Inc.) *Fibroblast growth factor-19*. WO 9927100.

SS-555

127149

6,6'-Di-*O*-octanoyl- α,α -trehalose

6-*O*-Octanoyl- α -D-glucopyranosyl α -D-glucopyranoside 6-octanoate



C28 H50 O13; Mol wt: 594.6900

ACTION – Antineoplastic agent, an inhibitor of TNF- α release (IC_{50} = 14.8 μ M against okadaic acid-induced TNF- α release in KATO III cells) able to inhibit TNF- α gene expression partly through inhibition of AP-1 activation. Compound significantly inhibited the promotion of murine skin tumors induced by DMBA + okadaic acid; when administered into mouse stomach, it inhibited the development of tumors in subcutaneous tissue and reduced serum levels of TNF- α , IL-1 and IL-6, indicating that it also inhibits cachexia in tumor-bearing animals. Potentially useful as a nontoxic lead compound for the development of chemopreventive agents.

SOURCES – Japan Tobacco; SSP.

REFERENCES

1. Fukushi, K. (SSP Co., Ltd.) *Antitumor formulation containing lipopolysaccharide with trehalose derivs*. US 4612304.
2. Kamiya, H. et al. (SSP Co., Ltd.) *Anticancer*. JP 86289038.
3. Nishikawa, Y. et al. (SSP Co., Ltd.) *α,α -Trehalose-6,6'-middle chained aliphatic acid diester and pharmaceutical agent containing the same*. DE 3241199, FR 2534259, GB 2133399.

4. Nishikawa, Y. et al. (SSP Co., Ltd.) *Preparation of α,α -trehalose-6,6'-fatty acid diester*. JP 83185599, JP 84181297.

5. Okabe, S. et al. *Disaccharide esters screened for inhibition of tumor necrosis factor- α release are new anti-cancer agents*. Jpn J Cancer Res 1999, 90(6): 669.

UBCLE

Ubiquitin-like conjugating protein

278254

ACTION – Human ubiquitin-like conjugating protein (UBCLE) expressed in cancer and developmental, immune and neuronal disorders and which plays a role in the degradation of cellular proteins in eukaryotic cells and some bacterial cells. Polynucleotides encoding this protein, as well as expression vectors, host cells, antibodies, agonists and antagonists are also provided. Also reported is the treatment or prevention of disorders associated with expression of UBCLE, particularly cancer and developmental, immune and neuronal disorders, by using antagonists thereof.

SOURCE – Incyte.

REFERENCES

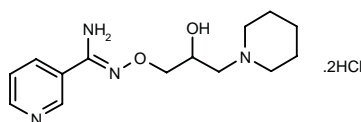
1. Hillman, J.L. et al. (Incyte Pharmaceuticals, Inc.) *Ubiquitin-like conjugating protein*. WO 9931252.

CHEMOPROTECTIVE AGENTS

BGP-15

278220

N'-[2-Hydroxy-3-(piperidin-1-yl)propoxy]pyridine-3-carboximidamide dihydrochloride



C14 H22 N4 O2 . 2HCl; Mol wt: 351.2756

ACTION – NAD⁺ ADP-ribosyltransferase (also known as poly[ADP] polymerase, poly[adenosine diphosphate ribose] polymerase and PARP) inhibitor proven to protect the heart from ischemia–reperfusion injury by decreasing the formation of endogenous reactive oxygen species (ROS) and by protecting DNA and cellular membranes from oxidative damage. Compound protected mice against ultraviolet B-induced acute skin damage and decreased the lethal toxic effects of cisplatin in mice without affecting its antitumor potency. Potentially useful as a chemoprotective agent.

SOURCES – Chinoïn; N-Gené.

REFERENCES

1. Bertók, B. et al. (Chinoin Pharmaceutical and Chemical Works Co., Ltd.) *Improved process for the preparation of amidoxime derivs.* WO 9008131.

2. Sümegi, B. (N-Gen Research Laboratories Inc.) *Pharmaceutical compsn. having enhanced antitumor activity and/or reduced side effects, containing an antitumor agent and an hydroxamic acid deriv.* WO 9858676.

3. Takacs, K. et al. (Chinoin Pharmaceutical and Chemical Works Co., Ltd.) *O-(3-Amino-2-hydroxy-propyl)amidoxime derivs., process for the preparation thereof and pharmaceutical compsns. containing same.* US 4308399.

4. Farkas, B. et al. *Protection against skin photodamage by a novel poly(ADP)-ribose polymerase (PARP) inhibitor.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst S54.2.

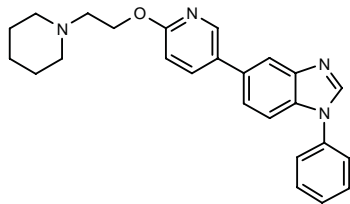
5. Szabados, E. et al. *BGP-15, a novel poly(ADP-ribose) polymerase inhibitor, protects heart from ischemia-reperfusion injury.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst S54.6.

6. Tóty, K. et al. *Chemoprotective effect of BGP-15 in combination with anti-tumor drugs.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst S54.5.

OCULAR MEDICATIONS

275814

1-Phenyl-5-[6-[2-(piperidin-1-yl)ethoxy]pyridin-3-yl]-1*H*-benzimidazole



C25 H26 N4 O; Mol wt: 398.5074

ACTION – An inhibitor of tyrosine kinases with selectivity for vascular endothelial growth factor (VEGF) receptor tyrosine kinase and potential particularly in the treatment of ocular neovascularization disorders such as diabetic retinopathy, as well as in the treatment of cancer.

SOURCE – Merck & Co.

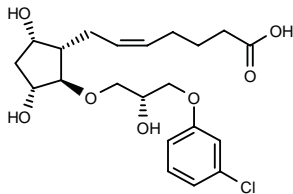
REFERENCES

1. Bilodeau, M.T. et al. (Merck & Co., Inc.) *Novel angiogenesis inhibitors.* WO 9916755.

278360

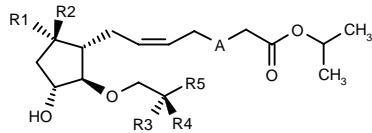
7-[(1*S*,2*R*,3*R*,5*S*)-2-[3-(3-Chlorophenoxy)-2(*R*)-hydroxypropoxy]-3,5-dihydroxycyclopentyl]-5(*Z*)-heptenoic acid

16-(3-Chlorophenoxy)-13,14-dihydro-17,18,19,20-tetranor-13-oxaprostaglandin F_{2α}



C21 H29 Cl O7; Mol wt: 428.9061

ACTION – Functional PGF_{2α} (FP), PGD₂ (DP) or PGE (EP) receptor agonist, potentially useful in the treatment of glaucoma and ocular hypertension. It is claimed to exhibit an improved therapeutic profile compared to natural prostaglandins and many analogues. Other specifically claimed 13-oxa-prostaglandins include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
278361	OH	H	OH	H	3-CF3-PhCH2CH2	CH2	C ₂₆ H ₃₇ F ₃ O ₆
278362		-O-	OH	H	CH2OPh	CH2	C ₂₄ H ₃₄ O ₇
278363	OH	H	H	OH	3-CF3-PhCH2CH2	CH2	C ₂₆ H ₃₇ F ₃ O ₆
278364	H	Cl	OH	H	cyclohexyl	O	C ₂₂ H ₃₇ ClO ₆

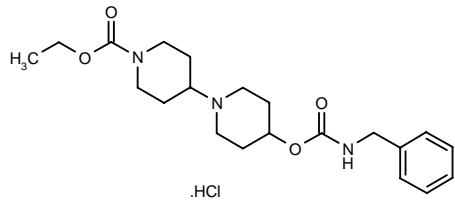
SOURCE – Alcon.

REFERENCES

1. Feng, Z. and Hellberg, M.R. (Alcon Laboratories, Inc.) *13-Oxa prostaglandins for the treatment of glaucoma and ocular hypertension.* WO 9932441.

278365

4-[4-(*N*-Benzylcarbamoyloxy)piperidin-1-yl]piperidine-1-carboxylic acid ethyl ester hydrochloride



C21 H31 N3 O4 . HCl; Mol wt: 425.9538

ACTION – Muscarinic compound useful for the treatment of glaucoma, myopia, dry eye, psychosis and pain. It is able to regulate intraocular pressure (IOP) and is more potent than pilocarpine in lowering IOP, while showing reduced miosis. It is also thought to be relatively free of other major side effects associated with pilocarpine therapy, such as impairment of accommodation.

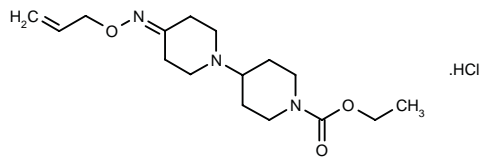
SOURCE – Alcon.

REFERENCES

1. Severns, B.S. et al. (Alcon Laboratories, Inc.) *Muscarinic agents and use thereof to treat glaucoma, myopia, and various other conditions.* WO 9932443.

278402

4-[4-(Allyloxyimino)piperidin-1-yl]piperidine-1-carboxylic acid ethyl ester hydrochloride



C16 H27 N3 O3 . HCl; Mol wt: 345.8682

REFERENCES

1. Bertók, B. et al. (Chinoin Pharmaceutical and Chemical Works Co., Ltd.) *Improved process for the preparation of amidoxime derivs.* WO 9008131.

2. Sümegi, B. (N-Gen Research Laboratories Inc.) *Pharmaceutical compsn. having enhanced antitumor activity and/or reduced side effects, containing an antitumor agent and an hydroxamic acid deriv.* WO 9858676.

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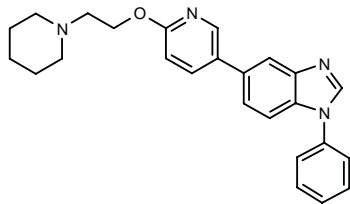
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OCULAR MEDICATIONS

275814

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SOURCE – Merck & Co.

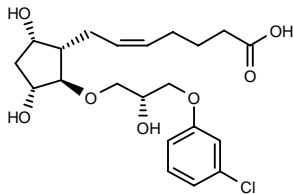
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278360

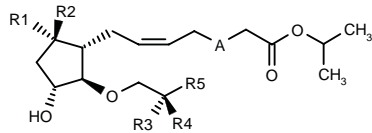
7-[(1*S*,2*R*,3*R*,5*S*)-2-[3-(3-Chlorophenoxy)-2(*R*)-hydroxypropoxy]-3,5-dihydroxycyclopentyl]-5(*Z*)-heptenoic acid

16-(3-Chlorophenoxy)-13,14-dihydro-17,18,19,20-tetranor-13-oxaprostaglandin F_{2α}



C21 H29 Cl O7; Mol wt: 428.9061

ACTION – Functional PGF_{2α} (FP), PGD₂ (DP) or PGE (EP) receptor agonist, potentially useful in the treatment of glaucoma and ocular hypertension. It is claimed to exhibit an improved therapeutic profile compared to natural prostaglandins and many analogues. Other specifically claimed 13-oxa-prostaglandins include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
278361	OH	H	OH	H	3-CF3-PhCH2CH2	CH2	C ₂₆ H ₃₇ F ₃ O ₆
278362		-O-	OH	H	CH2OPh	CH2	C ₂₄ H ₃₄ O ₇
278363	OH	H	H	OH	3-CF3-PhCH2CH2	CH2	C ₂₆ H ₃₇ F ₃ O ₆
278364	H	Cl	OH	H	cyclohexyl	O	C ₂₂ H ₃₇ ClO ₆

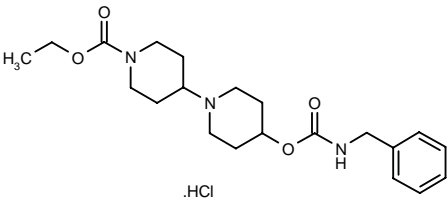
SOURCE – Alcon.

REFERENCES

1. Feng, Z. and Hellberg, M.R. (Alcon Laboratories, Inc.) *13-Oxa prostaglandins for the treatment of glaucoma and ocular hypertension.* WO 9932441.

278365

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C21 H31 N3 O4 . HCl; Mol wt: 425.9538

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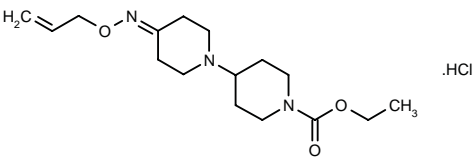
SOURCE – Alcon.

REFERENCES

1. Severns, B.S. et al. (Alcon Laboratories, Inc.) *Muscarinic agents and use thereof to treat glaucoma, myopia, and various other conditions.* WO 9932443.

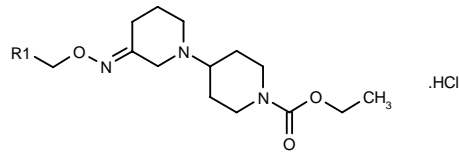
278402

4-[4-(Allyloxyimino)piperidin-1-yl]piperidine-1-carboxylic acid ethyl ester hydrochloride



C16 H27 N3 O3 . HCl; Mol wt: 345.8682

ACTION – Muscarinic agent particularly useful in the treatment of glaucoma by virtue of its ability to regulate intraocular pressure (IOP), being more potent than pilocarpine in lowering IOP while being associated with reduced miosis. Other exemplified compounds are:



Compound	R1	Formula
278403	Ph	C ₂₀ H ₂₉ N ₃ O ₃ .HCl
278404	H	C ₁₄ H ₂₅ N ₃ O ₃ .HCl

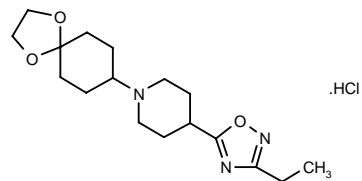
SOURCE – Alcon.

REFERENCES

1. Chen, H.-H. and Namil, A. (Alcon Laboratories, Inc.) *Oximino-piperidine, -pyrrolidine and -azepine derivs., their preparation and their use as muscarinic receptor antagonists.* WO 9932445.

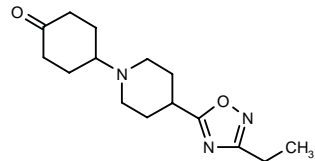
278416

1-(1,4-Dioxaspiro[4.5]dec-8-yl)-4-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine hydrochloride

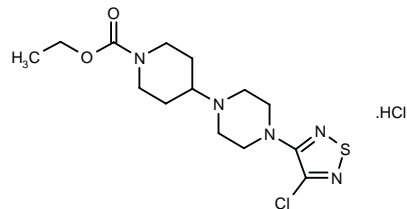


C17 H27 N3 O3 . HCl; Mol wt: 357.8792

ACTION – Muscarinic agent particularly useful in the treatment of glaucoma by virtue of its ability to regulate intraocular pressure (IOP), being more potent than pilocarpine in lowering IOP while being associated with reduced miosis. Other exemplified compounds are:



278417: C15 H23 N3 O2



278418: C14 H22 Cl N5 O2 S . HCl

SOURCE – Alcon.

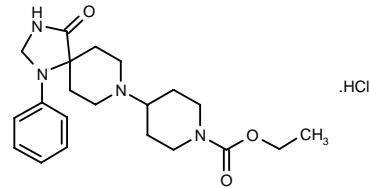
REFERENCES

1. Severns, B.S. et al. (Alcon Laboratories, Inc.) *Muscarinic agents and use thereof to treat glaucoma, myopia and various other conditions.* WO 9932486.

278419

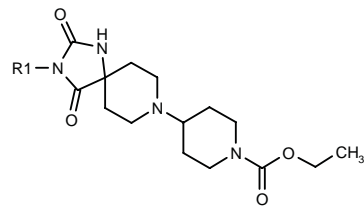
4-(4-Oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)piperidine-1-carboxylic acid ethyl ester hydrochloride

4-[5-Oxo-3-phenylspiro[imidazolidine-4,4'-piperidin]-1'-yl]piperidine-1-carboxylic acid ethyl ester hydrochloride

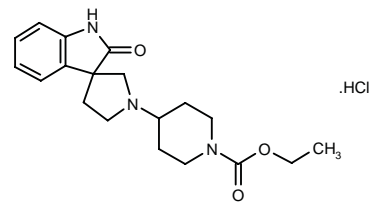


C21 H30 N4 O3 . HCl; Mol wt: 422.9539

ACTION – Muscarinic agent particularly useful in the treatment of glaucoma by virtue of its ability to regulate intraocular pressure (IOP), being more potent than pilocarpine in lowering IOP while being associated with reduced miosis. Other exemplified compounds are:



Compound	R1	Formula
278421	H	C ₁₅ H ₂₄ N ₄ O ₄
278422	2-thienyl	C ₁₉ H ₂₆ N ₄ O ₄ S



278420: C19 H25 N3 O3 . HCl

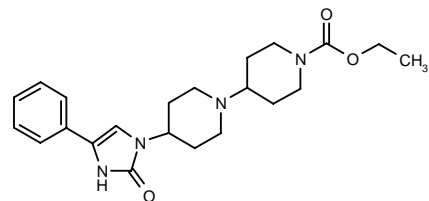
SOURCE – Alcon.

REFERENCES

1. Namil, A. et al. (Alcon Laboratories, Inc.) *Muscarinic agents and use thereof to treat glaucoma, myopia and various other conditions.* WO 9932489.

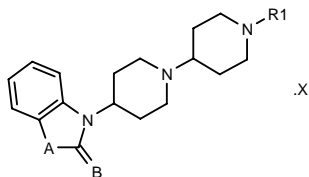
278439

4-[4-(2-Oxo-4-phenyl-2,3-dihydro-1H-imidazol-1-yl)piperidin-1-yl]piperidine-1-carboxylic acid ethyl ester

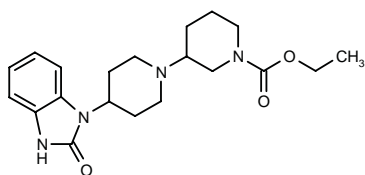


C22 H30 N4 O3; Mol wt: 398.5040

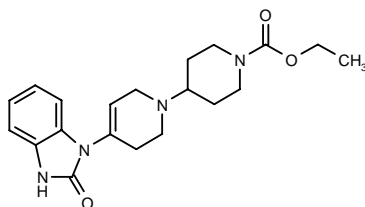
ACTION – Muscarinic compound useful for the treatment of glaucoma, myopia, dry eye, psychosis and pain. It is able to regulate intraocular pressure (IOP) and is more potent than pilocarpine in lowering IOP, while showing reduced miosis. It is also thought to be relatively free of other major side effects associated with pilocarpine therapy, such as impairment of accommodation. Other exemplified compounds are:



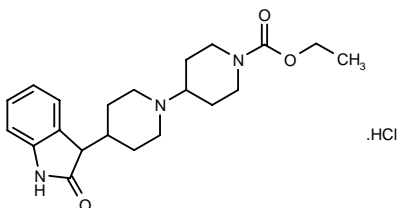
Compound	R1	A	B	X	Formula
278440	CO ₂ Et	NH	S		C ₂₀ H ₂₈ N ₄ O ₂ S
278443	CO ₂ Et	O	O	HCl	C ₂₀ H ₂₇ N ₃ O ₄ .HCl
278445	ethynyl-CH ₂ OCO	NH	O		C ₂₁ H ₂₆ N ₄ O ₃
278446	SO ₂ Me	NH	O	HCl	C ₁₈ H ₂₆ N ₄ O ₃ S.HCl



278441: C₂₀ H₂₈ N₄ O₃



278442: C₂₀ H₂₆ N₄ O₃



278444: C₂₁ H₂₉ N₃ O₃. HCl

SOURCE – Alcon.

REFERENCES

1. Namil, A. et al. (Alcon Laboratories, Inc.) *Muscarinic agents and use thereof to treat glaucoma, myopia and various other conditions*. WO 932481.

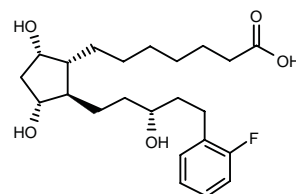
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

275384

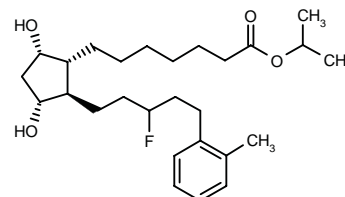
7-[(1*R*,2*R*,3*R*,5*S*)-2-[5-(2-Fluorophenyl)-3(*S*)-hydroxypentyl]-3,5-dihydroxycyclopentyl]heptanoic acid

17-(2-Fluorophenyl)-13,14-dihydro-18,19,20-trinorprostaglandin F_{1α}



C₂₃ H₃₅ F O₅; Mol wt: 410.5225

ACTION – Prostaglandin F analogue with potential in the treatment of bone disorders and glaucoma. Another exemplified compound from this series of aromatic C₁₆-C₂₀-substituted tetrahydroprostaglandins is:



275385: C₂₇ H₄₃ F O₄

SOURCE – Procter & Gamble.

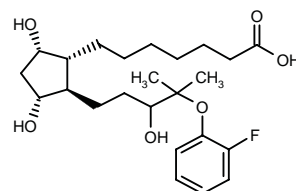
REFERENCES

1. Wos, J.A. et al. (The Procter & Gamble Co.) *Aromatic C₁₆-C₂₀-subst. tetrahydro prostaglandins useful as FP agonists*. WO 9912896.

275390

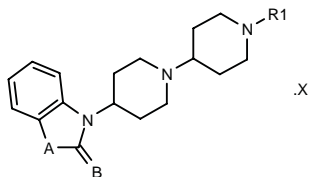
7-[(1*R*,2*R*,3*R*,5*S*)-2-[4-(2-Fluorophenoxy)-3-hydroxy-4-methylpentyl]-3,5-dihydroxycyclopentyl]heptanoic acid

16-(2-Fluorophenoxy)-16-methyl-13,14-dihydro-18,19,20-trinorprostaglandin F_{1α}

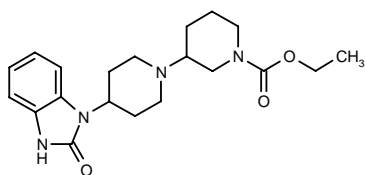


C₂₄ H₃₇ F O₆; Mol wt: 440.5483

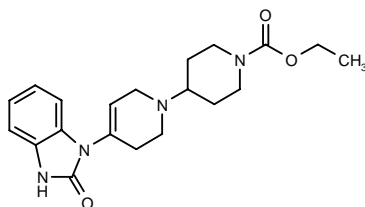
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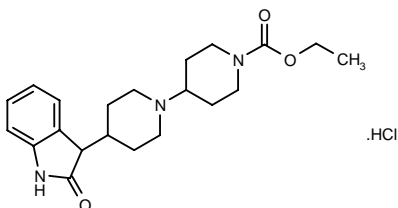
Compound	R1	A	B	X	Formula
278440	CO ₂ Et	NH	S		C ₂₀ H ₂₈ N ₄ O ₂ S
278443	CO ₂ Et	O	O	HCl	C ₂₀ H ₂₇ N ₃ O ₄ .HCl
278445	ethynyl-CH ₂ OCO	NH	O		C ₂₁ H ₂₆ N ₄ O ₃
278446	SO ₂ Me	NH	O	HCl	C ₁₈ H ₂₆ N ₄ O ₃ S.HCl



278441: C₂₀ H₂₈ N₄ O₃



278442: C₂₀ H₂₆ N₄ O₃



278444: C₂₁ H₂₉ N₃ O₃. HCl

SOURCE – Alcon.

REFERENCES

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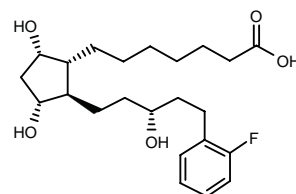
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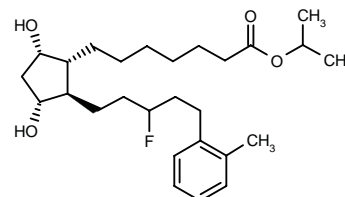
7-[(1*R*,2*R*,3*R*,5*S*)-2-[5-(2-Fluorophenyl)-3(*S*)-hydroxypentyl]-3,5-dihydroxycyclopentyl]heptanoic acid

17-(2-Fluorophenyl)-13,14-dihydro-18,19,20-trinorprostaglandin F_{1α}



C₂₃ H₃₅ F O₅; Mol wt: 410.5225

ACTION – Prostaglandin F analogue with potential in the treatment of bone disorders and glaucoma. Another exemplified compound from this series of aromatic C16-C20-substituted tetrahydroprostaglandins is:



275385: C₂₇ H₄₃ F O₄

SOURCE – Procter & Gamble.

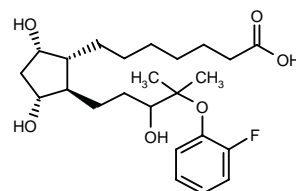
REFERENCES

1. Wos, J.A. et al. (The Procter & Gamble Co.) *Aromatic C16-C20-substd. tetrahydro prostaglandins useful as FP agonists*. WO 9912896.

275390

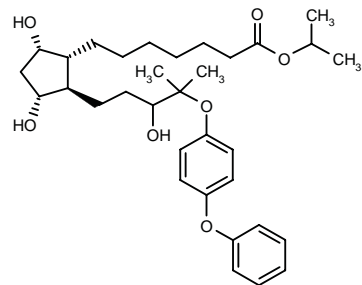
7-[(1*R*,2*R*,3*R*,5*S*)-2-[4-(2-Fluorophenoxy)-3-hydroxy-4-methylpentyl]-3,5-dihydroxycyclopentyl]heptanoic acid

16-(2-Fluorophenoxy)-16-methyl-13,14-dihydro-18,19,20-trinorprostaglandin F_{1α}



C₂₄ H₃₇ F O₆; Mol wt: 440.5483

ACTION – Prostaglandin F analogue with potential in the treatment of bone disorders and glaucoma. Another exemplified compound from this series of aromatic C16-C20-substituted tetrahydroprostaglandins is:



275391: C33 H48 O7

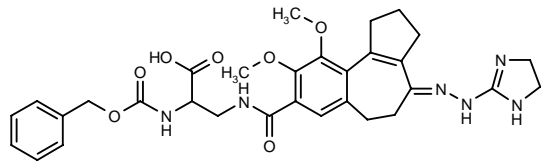
SOURCE – Procter & Gamble.

REFERENCES

1. Delong, M.A. et al. (The Procter & Gamble Co.) *Aromatic C16-C20-substd. tetrahydro prostaglandins useful as FP agonists.* WO 9912898.

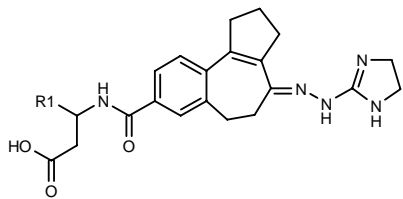
275686

2-(Benzyloxycarbonylamino)-3-[4(*E*)-[2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono]-9,10-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*e*]azulen-8-ylcarboxamido]propionic acid

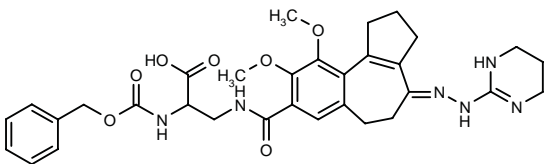


C31 H36 N6 O7; Mol wt: 604.6604

ACTION – Potent and selective vitronectin $\alpha_v\beta_3$ receptor antagonist (IC_{50} = 0.016 μ M) with the ability to inhibit osteoclast-mediated bone resorption. Potentially useful in the treatment of osteoporosis, rheumatoid arthritis, cancer and cardiovascular disorders. Within this series of tricyclic compounds, the following are also specifically claimed:



Compound	R1	Formula
275688	3-Pyr	C ₂₆ H ₂₈ N ₆ O ₃
275689	1,3-benzodioxol-5-yl	C ₂₈ H ₂₉ N ₅ O ₅



275687: C32 H38 N6 O7

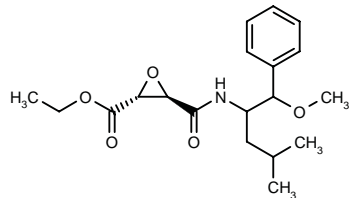
SOURCES – Genentech; Hoechst Marion Roussel.

REFERENCES

1. Carniato, D. et al. (Genentech, Inc.;Hoechst Marion Roussel, SA) *Tricyclic cpds., preparation method and said method intermediates, application as medicines and pharmaceutical compsns. containing same.* FR 2768736, WO 9915506.

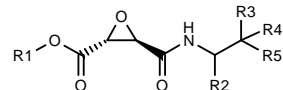
275898

trans-3-[*N*-(1-Isobutyl-2-methoxy-2-phenylethyl)carbamoyl]oxirane-2-carboxylic acid ethyl ester



C19 H27 N O5; Mol wt: 349.4243

ACTION – Agent for the treatment of osteoporosis and arthritis proven to inhibit bone resorption in rats fed a low-calcium diet, as measured by a 20.4% decrease in plasma calcium concentration when given at 15 mg/kg p.o.; it also increased bone density of the fourth lumbar in ovariectomized rats when given at 300 mg/kg/day p.o. x 4 weeks. In addition, it produced 42% inhibition of paw swelling in a rat adjuvant-induced arthritis model at 300 mg/kg/day p.o. x 3 weeks. Other representative compounds within this series of epoxysuccinamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
275899	Et	i-Bu	Ph	OH	H	C ₁₈ H ₂₅ NO ₅
275900	Et	i-Bu	Ph	-O-		C ₁₈ H ₂₃ NO ₅
275901	Et	i-Pr	Ph	-O-		C ₁₇ H ₂₁ NO ₅
275902	H	i-Bu	Ph	OMe	H	C ₁₇ H ₂₃ NO ₅
275903	Et	i-Bu	Ph	OAc	H	C ₂₀ H ₂₇ NO ₆
275904	i-Pr	i-Bu	Ph	OMe	H	C ₂₀ H ₂₉ NO ₅
275905	Et	i-Bu	H	OCH2Ph	H	C ₁₉ H ₂₇ NO ₅
275906	Et	i-Bu	H	i-BuO	H	C ₁₆ H ₂₉ NO ₅

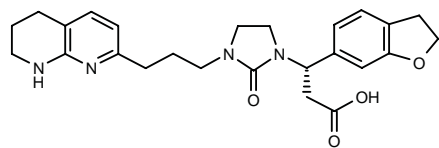
SOURCE – Nippon Chemiphar.

REFERENCES

1. Nomura, Y. et al. (Nippon Chemiphar Co., Ltd.) *Epoxysuccinamide derivs.* WO 9911640.

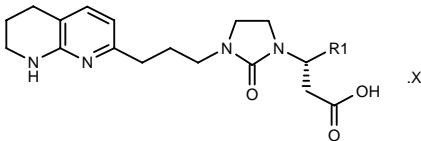
277981

3(*S*)-(2,3-Dihydrobenzofuran-6-yl)-3-[2-oxo-3-[3-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)propyl]imidazolidin-1-yl]propionic acid



C25 H30 N4 O4; Mol wt: 450.5360

ACTION – Integrin $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptor antagonist specifically claimed for use in inhibiting bone resorption and tumor growth, as well as for the treatment of restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation and viral disease. Other specifically claimed compounds are:



Compound	R1	X	Formula
277982	3-quinolinyl		C ₂₆ H ₂₉ N ₅ O ₃
277983	3-Pyr		C ₂₂ H ₂₇ N ₅ O ₃
277984	6-MeO-3-Pyr		C ₂₃ H ₂₉ N ₅ O ₄
277985	6-EtO-3-Pyr		C ₂₄ H ₃₁ N ₅ O ₄
277986	4-MeO-7-quinolinyl	2CF ₃ CO ₂ H	C ₂₇ H ₃₁ N ₅ O ₄ .2C ₂ HF ₃ O ₂
277987	6-(MeNH)-3-Pyr		C ₂₃ H ₃₀ N ₆ O ₃
277988	4-EtO-3-F-Ph		C ₂₅ H ₃₁ FN ₅ O ₄
277989	furo[2,3-b]pyridin-6-yl		C ₂₄ H ₂₇ N ₅ O ₄
277990	furo[3,2-b]pyridin-6-yl		C ₂₄ H ₂₇ N ₅ O ₄
277991	2-benzimidazolyl		C ₂₄ H ₂₈ N ₆ O ₃
277992	2-benzoxazolyl		C ₂₄ H ₂₇ N ₅ O ₄

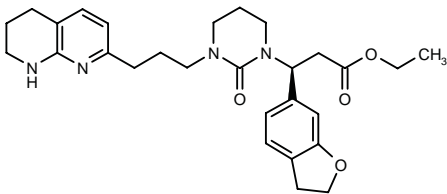
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. et al. (Merck & Co., Inc.) *Integrin receptor antagonists*. WO 9931099.

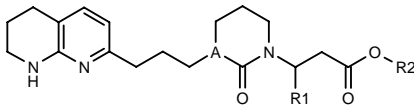
277999

3(S)-(2,3-Dihydrobenzofuran-6-yl)-3-[2-oxo-3-[3-(5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)propyl]perhydropyrimidin-1-yl]propionic acid ethyl ester



C₂₈ H₃₆ N₄ O₄; Mol wt: 492.6164

ACTION – Integrin $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptor antagonist specifically claimed for use in inhibiting bone resorption and tumor growth, as well as for the treatment of restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation and viral disease. Other specifically claimed compounds are:



Compound	R1	R2	A	Isomer	Formula
278000	3-F-Ph	Et	CH	A	C ₂₇ H ₃₄ FN ₃ O ₃
278001	3-F-Ph	Et	CH	B	C ₂₇ H ₃₄ FN ₃ O ₃
278002	2,3-dihydro-6-benzofuryl	H	N	(S)	C ₂₆ H ₃₂ N ₄ O ₄
278003	3-F-Ph	H	CH	A	C ₂₅ H ₃₀ FN ₃ O ₃
278004	3-F-Ph	H	CH	B	C ₂₅ H ₃₀ FN ₃ O ₃

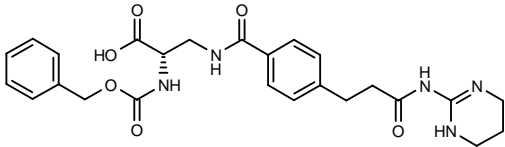
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. et al. (Merck & Co., Inc.) *Integrin receptor antagonists*. WO 9930713.

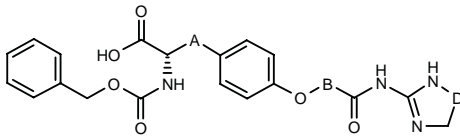
278272

2(S)-(Benzyloxycarbonylamino)-3-[4-[2-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]ethyl]benzamido]-propionic acid



C₂₅ H₂₉ N₅ O₆; Mol wt: 495.5331

ACTION – Bone resorption inhibitor with vitronectin receptor-antagonist activity (IC₅₀ = 0.017 μ M for inhibition of the vitronectin $\alpha_v\beta_3$ receptor in human embryonic kidney 293 cells). Potentially useful for the treatment of osteoporosis, for inhibiting tumor growth or metastasis, as an antiinflammatory drug or for the therapy or prophylaxis of cardiovascular disorders, restenosis, atherosclerosis, nephropathies or retinopathies. Other specifically claimed acylguanidine derivatives are:



Compound	A	B	D	Formula
278273	-CH ₂ -	-(CH ₂) ₃ -	-(CH ₂) ₂ -	C ₂₅ H ₃₀ N ₄ O ₆
278274	-CH ₂ NHCO-	-CH ₂ -	-(CH ₂) ₂ -	C ₂₄ H ₂₇ N ₅ O ₇
278275	-CH ₂ -	-(CH ₂) ₃ -	-CH ₂ -	C ₂₄ H ₂₈ N ₄ O ₆

SOURCES – Genentech; Hoechst Marion Roussel.

REFERENCES

1. Peyman, A. et al. (Hoechst Marion Roussel Deutschland GmbH;Genentech, Inc.) *Novel acylguanidine derivs. as inhibitors of bone resorption and as vitronectin receptor antagonists*. EP 933367, WO 9932457.

BMP-17

277851*Bone morphogenetic protein 17*

ACTION – Human bone morphogenetic protein with potential for inducing bone and/or cartilage or other connective tissue formation, in wound healing and tissue repair, as well as for enhancing the activity of other bone morphogenetic proteins. Another related protein is:

*Bone morphogenetic protein 18***277853****SOURCE** – Genetics Institute.

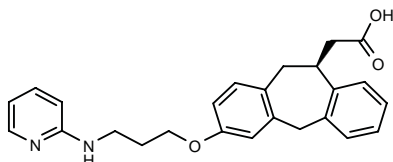
REFERENCES

1. Celeste, A.J. and Murray, B.L. (Genetics Institute Inc.) *Bone morphogenetic protein (BMP)-17 and BMP-18 compsns.* WO 9929718.

SB-265123

278078

2-[3-[3-(Pyridin-2-ylamino)propoxy]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-10(R)-yl]acetic acid



C25 H26 N2 O3; Mol wt: 402.4914

ACTION – Integrin $\alpha_v\beta_3$ (vitronectin) receptor antagonist ($K_i = 4$ nM) with high affinity also for the $\alpha_v\beta_5$ subtype receptor ($K_i = 1.3$ nM) and > 1000-fold selectivity over gpIIb/IIIa and $\alpha_5\beta_1$ receptors ($K_i = 9$ and 18 μ M, respectively). Compound was able to inhibit $\alpha_v\beta_3$ -mediated cell adhesion ($IC_{50} = 60$ nM) but did not inhibit human ADP-induced platelet aggregation ($IC_{50} > 200$ μ M). It was a potent inhibitor of bone resorption both *in vitro* ($IC_{50} = 48$ nM in human osteoclast resorption assay) and *in vivo*; in the thyroparathyroidectomized rat model of bone resorption, continuous i.v. infusion of compound (2.53 mg/kg/h) gave 85% inhibition of calcemic response after 6 h, and in the ovariectomized rat model of osteoporosis, it significantly and dose-dependently (3-30 mg/kg p.o.) inhibited bone loss. Compound showed a good pharmacokinetic profile with an oral bioavailability of about 100% and a plasma half-life of 181-378 min in rats. Potentially useful for the treatment of osteoporosis, restenosis following coronary angioplasty and diseases involving neovascularization.

SOURCE – SmithKline Beecham.

REFERENCES

1. Bondinell, W.E. et al. (SmithKline Beecham Corp.) *Vitronectin receptor antagonists.* WO 9915508.

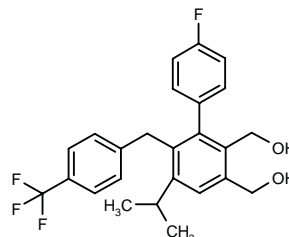
2. Drake, F.H. (SmithKline Beecham plc) *Method for stimulating bone formation.* EP 946180, WO 9815278.

3. Miller, W.H. et al. *Orally bioavailable nonpeptide vitronectin receptor antagonists with efficacy in an osteoporosis model.* Bioorg Med Chem Lett 1999, 9(13): 1807.

TREATMENT OF LIPOPROTEIN DISORDERS

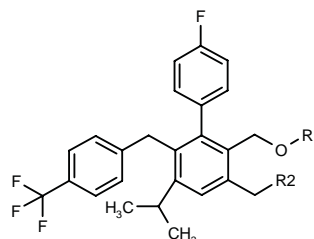
275657

[4'-Fluoro-5-isopropyl-6-[4-(trifluoromethyl)benzyl]-biphenyl-2,3-diyl]bismethanol



C25 H24 F4 O2; Mol wt: 432.4546

ACTION – Agent for the treatment of dyslipidemia, hypertriglyceridemia, hyperlipidemia and arteriosclerosis, an inhibitor of cholesteryl ester transfer protein (CETP). Other compounds from this series of benzyl-biphenyl derivatives include the following:



Compound	R1	R2	Formula
275658	2-THP	OH	C ₃₀ H ₃₂ F ₄ O ₃
275659	H	OCH ₂ Ph	C ₃₂ H ₃₀ F ₄ O ₂
275660	H	4-F-PhO	C ₃₁ H ₂₇ F ₅ O ₂
275661	H	1,3-dioxo-2-isindolyl	C ₃₃ H ₂₇ F ₄ NO ₃
275662	H	cyclopentylidene	C ₃₀ H ₃₀ F ₄ O
275663	H	cyclopentyl	C ₃₀ H ₃₂ F ₄ O

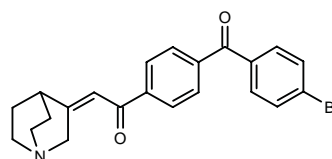
SOURCE – Bayer.

REFERENCES

1. Lögers, M. et al. (Bayer AG) *Benzyl-biphenyls and analogous cpds. and the application thereof in order to treat arteriosclerosis and dyslipidaemia.* DE 19741400, WO 9915487.

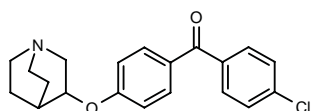
276975

(Z)-2-(1-Azabicyclo[2.2.2]oct-3-ylidene)-1-[4-(4-bromobenzoyl)phenyl]ethanone



C22 H20 Br N O2; Mol wt: 410.3090

ACTION – Hypocholesterolemic agent, an inhibitor of cholesterol biosynthesis that acts by inhibiting lanosterol synthase (IC_{50} = 83 and 124 nM, respectively, against enzyme from human and rat microsomes). *In vivo*, compound inhibited cholesterol biosynthesis in rats with an ED_{50} of 1.3 mg/kg p.o. and in marmosets complete inhibition was achieved at 15 mg/kg p.o. Another related compound is:



276976: C₂₀ H₂₀ Cl N O₂

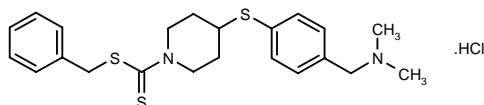
SOURCE – AstraZeneca.

REFERENCES

1. Brown, G.R. et al. Quinuclidine inhibitors of 2,3-oxidosqualene cyclase-lanosterol synthase: Optimization from lipid profiles. *J Med Chem* 1999, 42(7): 1306.

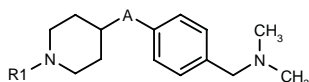
277864

4-[4-(Dimethylaminomethyl)phenylsulfanyl]piperidine-1-carbodithioic acid benzyl ester hydrochloride

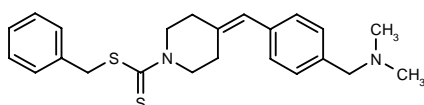


C₂₂ H₂₈ N₂ S₃ . HCl; Mol wt: 453.1361

ACTION – Cholesterol biosynthesis inhibitor that acts by inhibiting lanosterol synthase activity. Potentially useful in the treatment of hyperlipidemia, hypercholesterolemia, atherosclerosis, hyperproliferative disorders, tumors and fungal infections. Other specifically claimed urethanes are:



Compound	R1	A	Formula
277866	CS ₂ CH ₂ Ph	CO	C ₂₃ H ₂₈ N ₂ O ₂ S ₂
277867	CO ₂ CH ₂ Ph	S	C ₂₂ H ₂₈ N ₂ O ₂ S
277869	4-Cl-PhOCO	S	C ₂₁ H ₂₅ ClN ₂ O ₂ S
277870	CS ₂ CH ₂ Ph	CH ₂	C ₂₃ H ₃₀ N ₂ S ₂
277872	4-Cl-PhOCS	CH ₂	C ₂₂ H ₂₇ ClN ₂ O ₂ S
277873	4-Cl-PhOCO	CH ₂	C ₂₂ H ₂₇ ClN ₂ O ₂
277875	CO ₂ CH ₂ Ph	CH ₂	C ₂₃ H ₃₀ N ₂ O ₂
277876	4-Me-PhOCO	CH ₂	C ₂₃ H ₃₀ N ₂ O ₂
277877	4-Me-PhOCS	CH ₂	C ₂₃ H ₃₀ N ₂ OS
277878	4-F-PhOCO	CH ₂	C ₂₂ H ₂₇ FN ₂ O ₂



277871: C₂₃ H₂₈ N₂ S₂

SOURCE – Boehringer Ingelheim.

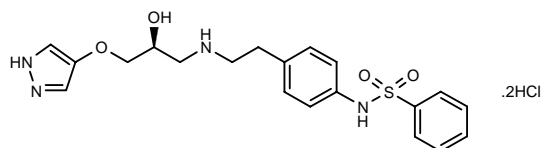
REFERENCES

1. Maier, R. et al. (Boehringer Ingelheim Pharma KG) Urethanes derived from azacycloalkanes, thio and dithio analogues, production and use thereof as 2,3 epoxysqualene lanosterol cyclase inhibitors. DE 19754796, WO 9929669.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

277808

N-[4-[2-[2(S)-Hydroxy-3-(1H-pyrazol-4-yloxy)propyl-amino]ethyl]phenyl]benzenesulfonamide dihydrochloride



C₂₀ H₂₄ N₄ O₄ S . 2HCl; Mol wt: 489.4214

ACTION – Potent and selective β_3 -adrenoceptor agonist useful in the treatment of obesity and type II diabetes, shown to exhibit marked effects on lipolysis, thermogenesis and serum glucose levels in animal models of type II diabetes.

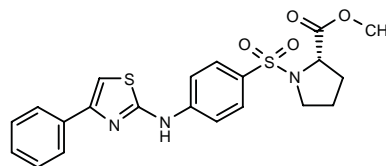
SOURCE – Lilly.

REFERENCES

1. Crowell, T.A. et al. (Eli Lilly and Company) Selective β_3 adrenergic agonists. WO 9929672.

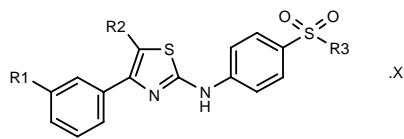
278366

N-[4-(4-Phenylthiazol-2-ylamino)phenylsulfonyl]-L-proline methyl ester



C₂₁ H₂₁ N₃ O₄ S₂; Mol wt: 443.5459

ACTION – Antiobesity agent with high and selective affinity for the neuropeptide Y (NPY) Y_5 receptor subtype and antagonist activity at this receptor *in vitro* and *in vivo*. It inhibited NPY-induced increases in calcium in stably transfected cells expressing the Y_5 receptor and the intake of food in rats induced by NPY or food withdrawal for 24 h. Other exemplified benzenesulfonamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
278367	H	H	2(S)-(MeOCH2)- -1-pyrrolidinyl		C ₂₁ H ₂₃ N ₃ O ₃ S ₂
278368	H	H	NHEt		C ₁₇ H ₁₇ N ₃ O ₂ S ₂
278369	H	H	NHMe		C ₁₆ H ₁₅ N ₃ O ₂ S ₂
278370	H	H	2(S)-(MeSO2CH2)- -1-pyrrolidinyl	HCl	C ₂₁ H ₂₃ N ₃ O ₄ S ₃ ·HCl
278371	F	Cl	NHMe		C ₁₆ H ₁₃ ClFN ₃ O ₂ S ₂

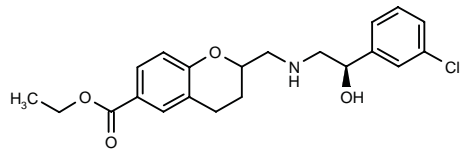
SOURCE – Novartis.

REFERENCES

1. Buehlmayer, P. (Novartis AG) *Substd. benzenesulfonamide derivs. and their pharmaceutical use.* WO 9932466.

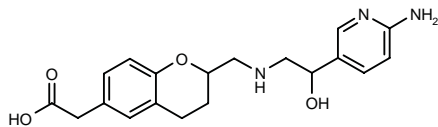
278423

2-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylaminomethyl]-3,4-dihydro-2*H*-1-benzopyran-6-carboxylic acid ethyl ester



C21 H24 Cl N O4; Mol wt: 389.8766

ACTION – Selective β₃-adrenoceptor agonist expected to be of value as a therapeutic agent in the treatment of obesity, diabetes, gastrointestinal disorders, neurogenic inflammation and depression. Another representative compound from this series of carboxyl substituted chroman derivatives is:



278424: C19 H23 N3 O4

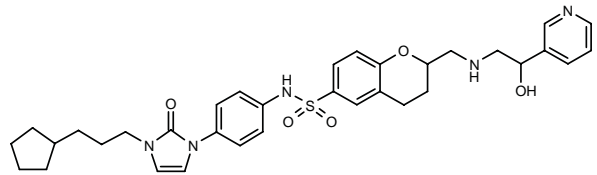
SOURCE – Bayer.

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1. Connell, R.D. et al. (Bayer Corp.) *Carboxyl substd. chroman derivs. useful as β₃ adrenoceptor agonists.* WO 9932476.

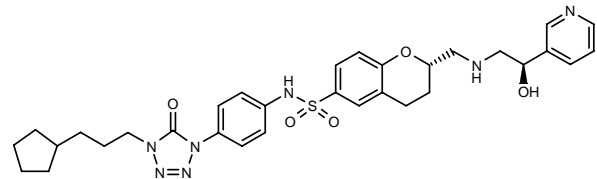
278425

N-[4-[3-(3-Cyclopentylpropyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]phenyl]-2-[2-hydroxy-2-(pyridin-3-yl)-ethylaminomethyl]-3,4-dihydro-2*H*-1-benzopyran-6-sulfonamide



C34 H41 N5 O5 S; Mol wt: 631.7939

ACTION – Selective β₃-adrenoceptor agonist without β₁- and/or β₂-adrenoceptor-mediated effects, and therefore expected to be useful in the treatment of obesity and diabetes, as well as irritable bowel syndrome, intestinal hypermotility disorders, peptic ulcer, esophagitis, gastritis, duodenitis, inflammatory bowel disease, ulcerative colitis, Crohn’s disease, cough, asthma and depression. Another representative compound from this series of sulfonamide derivatives is:



278426: C32 H39 N7 O5 S

SOURCE – Bayer.

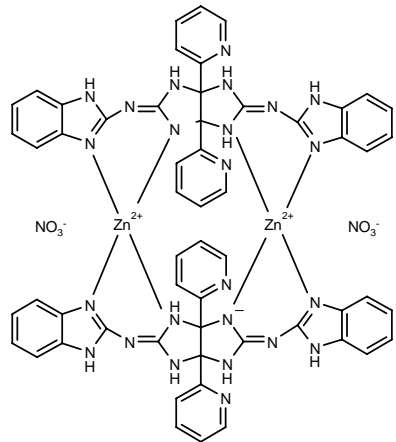
REFERENCES

1. Ladouceur, G.H. et al. (Bayer Corp.) *Novel sulfonamide substd. chroman derivs. useful as β₃ adrenoceptor agonists.* WO 9932475.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

276738

Bis[μ-*[N,N'*-bis(1*H*-benzimidazol-2-yl-κ*N*³)-1,3a,4,6a-tetrahydro-3a-(2-pyridinyl)-6a-(2-pyridinyl-κ*N*)imidazo-[4,5-*d*]imidazole-2,5-diamidato-κ*N*¹:κ*N*⁶]]dizinc(2+) dini-
trate



C56 H42 N24 Zn2 . 2NO3; Mol wt: 1305.9040

ACTION – Novel metal complex of a known granulocyte colony-stimulating factor (G-CSF) mimetic* for use as a G-CSF receptor agonist. The metal-chelated compound showed greatly improved activity as compared to the nonchelated form, as demonstrated in a luciferase assay using NFS60 cells, where it showed activation above 350% of control at 1 μ M compared to activation above 150% for the nonchelated compound in the concentration range 1-100 μ M. Potentially useful for the treatment of neutropenia including chemotherapy-induced neutropenia, and in bone marrow transplantation, as well as for the treatment of bacterial and fungal infections.

SOURCES – Ligand; SmithKline Beecham.

REFERENCES

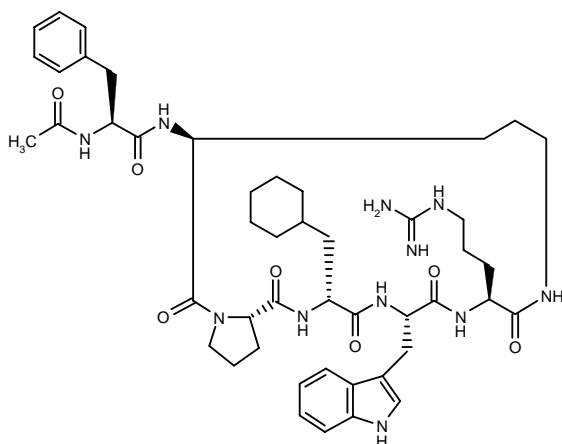
1. Luengo, J.I. et al. (SmithKline Beecham Corp.;Ligand Pharmaceuticals, Inc.) *Novel metal complexes*. WO 9922732, WO 9922733, WO 9922734.

*See **SB-247464** Drug Data Reo 1998, 020(09): 0812.

277544

(3*S*,9*S*,12*S*,15*R*,18*S*)-3-(*N*-Acetyl-L-phenylalanyl-amino)-15-(cyclohexylmethyl)-9-(3-guanidinopropyl)-12-(1*H*-indol-3-ylmethyl)-1,7,10,13,16-pentaazabicyclo-[16.3.0]heneicosane-2,8,11,14,17-pentaone

N-Acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-D-arginine *N*-5.2-*C*-1.6-lactam



C47 H65 N11 O7; Mol wt: 896.1005

ACTION – Complement factor C5a receptor antagonist with high affinity (IC_{50} = 0.3 μ M against [125 I]-C5a binding to intact human polymorphonuclear leukocytes [PMNs]) and antagonist activity in functional studies (IC_{50} = 20 nM against C5a-induced myeloperoxidase release in PMNs). In rats, compound given i.v. or p.o. significantly inhibited neutropenia induced by cobra venom factor and C5a. Also potentially useful for the treatment of inflammatory diseases associated with elevated C5a levels such as rheumatoid arthritis, adult respiratory distress syndrome, Alzheimer's disease and ischemic heart failure.

SOURCE – University of Queensland, St. Lucia (AU).

REFERENCES

1. Fairlie, D. et al. (University of Queensland) *Cyclic agonists and antagonists of C5a receptors and G protein-coupled receptors*. WO 9900406.

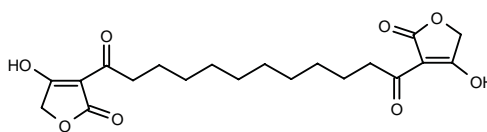
2. Finch, A.M. et al. *Low-molecular-weight peptidic and cyclic antagonists of the receptor for the complement factor C5a*. J Med Chem 1999, 42(11): 1965.

3. Paczkowski, N. et al. *In vivo activity of a C5a receptor antagonist*. Mediators Inflamm 1999, 8(Suppl. 1): Abst P-11-1.

4. Wong, A.K. et al. *Small molecular probes for G-protein-coupled C5a receptors: Conformationally constrained antagonists derived from the C terminus of the human plasma protein C5a*. J Med Chem 1998, 41(18): 3417.

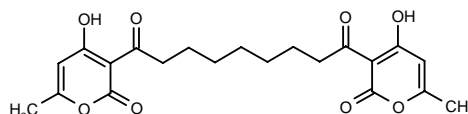
278073

1,12-Bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)do-decane-1,12-dione



C20 H26 O8; Mol wt: 394.4174

ACTION – Hematopoietic cell phosphatase (HCP) inhibitor (IC_{50} = 39 μ M) with potential in the treatment of hemocytopenia. Another compound from this series of lactone derivatives is:



278074: C21 H24 O8

SOURCE – Toray.

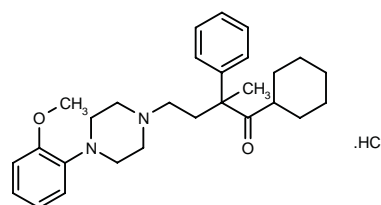
REFERENCES

1. Sugawara, Y. et al. (Toray Industries, Inc.) *Lactone derivs. and their medicinal use*. JP 99130767.

TREATMENT OF POISONING AND DRUG DEPENDENCY

277801

(+)-1-Cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-methyl-2-phenylbutan-1-one hydrochloride



C28 H38 N2 O2 . HCl; Mol wt: 471.0811

ACTION – Novel metal complex of a known granulocyte colony-stimulating factor (G-CSF) mimetic* for use as a G-CSF receptor agonist. The metal-chelated compound showed greatly improved activity as compared to the nonchelated form, as demonstrated in a luciferase assay using NFS60 cells, where it showed activation above 350% of control at 1 μ M compared to activation above 150% for the nonchelated compound in the concentration range 1-100 μ M. Potentially useful for the treatment of neutropenia including chemotherapy-induced neutropenia, and in bone marrow transplantation, as well as for the treatment of bacterial and fungal infections.

SOURCES – Ligand; SmithKline Beecham.

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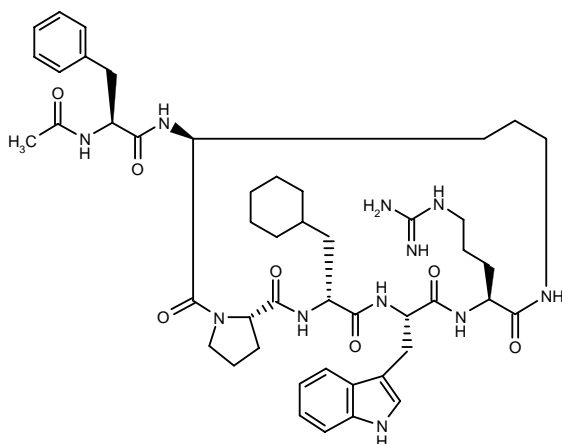
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*See **SB-247464** Drug Data Reo 1998, 020(09): 0812.

277544

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C47 H65 N11 O7; Mol wt: 896.1005

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SOURCE – University of Queensland, St. Lucia (AU).

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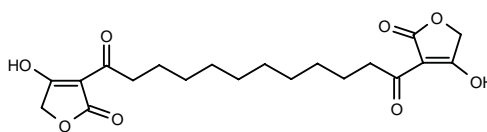
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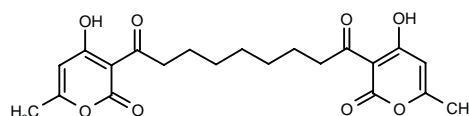
278073

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278074: C21 H24 O8

SOURCE – Toray.

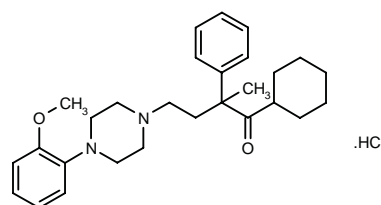
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TREATMENT OF POISONING AND DRUG DEPENDENCY

277801

(+)-1-Cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-methyl-2-phenylbutan-1-one hydrochloride



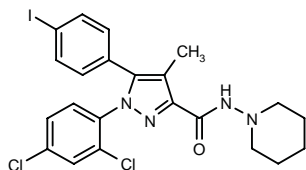
C28 H38 N2 O2 . HCl; Mol wt: 471.0811

4'-I-SR-141716A

277072

1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-(1-piperidinyl)-1H-pyrazole-3-carboxamide

AM-251



C22 H21 Cl2 I N4 O; Mol wt: 555.2409

White solid, m.p. 195-6 °C.

ACTION – Potent and selective cannabinoid CB₁ receptor antagonist (K_i = 7.49 and 2290 nM, respectively, for CB₁ and CB₂ receptors) with functional antagonist activity in guinea pig myenteric plexus-longitudinal muscle preparations and mouse vas deferens (K_d = 0.22 and 0.50 nM, respectively). Because of its iodinated nature, compound represents an effective probe for single-photon emission computed tomography (SPECT) for characterizing brain CB₁ receptors *in vivo*.

SOURCES – University of Aberdeen, Aberdeen (GB); University of Connecticut, Storrs, CT (US); Research Triangle Institute, Research Triangle Park, NC (US).

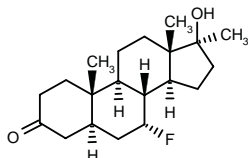
REFERENCES

1. Gatley, S.J. et al. *Imaging the brain marijuana receptor: Development of a radioligand that binds to cannabinoid CB1 receptors in vivo*. J Neurochem 1998, 70(1): 417.
2. Lan, R. et al. *Preparation of iodine-123 labeled AM251: A potential SPECT radioligand for the brain cannabinoid CB1 receptor*. J Label Compd Radiopharm 1996, 38(10): 875.
3. Lan, R. et al. *Structure-activity relationships of pyrazole derivatives as cannabinoid receptor antagonists*. J Med Chem 1999, 42(4): 769.
4. Thomas, B.F. et al. *Comparative receptor binding analyses of cannabinoid agonists and antagonists*. J Pharmacol Exp Ther 1998, 285(1): 285.

F-17α-CH3-DHT

277083

17β-Hydroxy-7α-fluoro-17-methyl-5α-androstan-3-one



C20 H31 F O2; Mol wt: 322.4609

M.p. 206-10 °C.

ACTION – Androgen receptor agonist with binding affinity and androgenic activity superior to 5α-dihydrotestosterone (5α-DHT; relative binding affinity = 123 and relative androgenic activity = 418 vs. 100 for 5α-DHT). Compound showed high stability in aqueous solution at 37 °C. Compound labeled with ¹⁸F is expected to be an excellent PET probe for androgen receptor-mediated imaging of prostate tumors and metastases.

SOURCES – Baylor College of Medicine, Houston, TX (US); State University of New York, Albany, NY (US); Yale University, New Haven, CT (US).

REFERENCES

1. Labaree, D.C. et al. *2alpha-Iodo and 2alpha-fluoro steroids as androgen receptor-mediated imaging agents*. J Med Chem 1999, 42(11): 2021.

SDF1-3'A

276678

Nucleic acid sequence having a single nucleotide mutation in the 3'-untranslated region on the mRNA transcript of the structural gene for stromal cell-derived factor

ACTION – Polynucleotide encoding a stromal cell-derived factor (SDF-1) variant having a mutation in the 3'-untranslated region of the mRNA transcript of the SDF-1 structural gene that is associated with resistance to or decreased susceptibility to HIV infection. Compound is thus potentially useful for determining the prognosis of a subject exposed to HIV-1, as well as the susceptibility of a subject to HIV-1 infection.

SOURCE – Dept. of Health & Human Services (US).

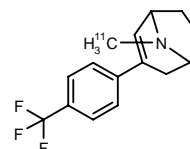
REFERENCES

1. Winkler, C.A. and O'Brien, S.J. (Department of Health & Human Services) *Stromal cell derived factor-1 (SDF1) and method of use for diagnostic and prognostic indicator of AIDS pathogenesis*. WO 9923253.

[¹¹C]-NS-2381

278427

8-([¹¹C]Methyl)-3-[4-(trifluoromethyl)phenyl]-8-azabicyclo[3.2.1]oct-2-ene



C15 H16 F3 N; Mol wt: 266.2814

ACTION – Potent and selective 5-HT reuptake inhibitor that in [¹¹C]-radiolabeled form accumulates readily in the brain and binds reversibly in regions rich in 5-HT uptake sites; compound was displaced from brain tissues by the potent 5-HT reuptake inhibitor citalopram. Potentially useful as a PET (positron emission tomography) radioligand for studying 5-HT uptake sites in the living brain.

SOURCE – NeuroSearch.

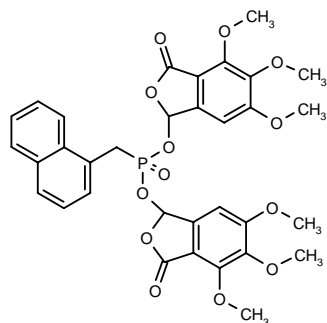
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1. Moldt, P. et al. (NeuroSearch A/S) *8-Azabicyclo[3.2.1]oct-2-ene derivs. in labelled and use of 8-azabicyclo[3.2.1]oct-2-ene derivs. in labelled and unlabelled form*. WO 9938866.
2. Moldt, P. et al. (NeuroSearch A/S) *8-Azabicyclo[3.2.1]oct-2-ene derivs., their preparation and use*. EP 859777, JP 98512589, WO 9713770.
3. Smith, D.F. et al. *[¹¹C]NS2381 and enantiomers: New selective serotonin reuptake inhibitors studied by PET in living porcine brain*. J Cereb Blood Flow Metab 1999, 19(Suppl. 1): Abstr 796.

DRUG DELIVERY

277388

(1-Naphthyl)methylphosphonic acid 4,5,6-trimethoxy-3-oxo-1,3-dihydrobenzofuran-1-yl diester



C33 H31 O13 P; Mol wt: 666.5689

ACTION – A 3-phthalidyl ester prodrug of 1-naphthalene-methylphosphonate (NMPA) with improved plasma half-life ($t_{1/2}$ = 5 min), plasma stability and safety (it does not generate formaldehyde) over traditional acycloxymethyl prodrugs.

SOURCE – Metabasis.

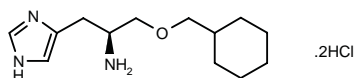
REFERENCES

1. Dang, Q. et al. *Synthesis of phosphonate 3-phthalidyl esters as prodrugs for potential intracellular delivery of phosphonates*. Bioorg Med Chem Lett 1999, 9(11): 1505.

PHARMACOLOGICAL TOOLS

271929

1-(Cyclohexylmethoxy)-3-(1*H*-imidazol-4-yl)propane-2(*S*)-amine dihydrochloride



C13 H23 N3 O . 2HCl; Mol wt: 310.2665

White crystals, m.p. 255 °C.

ACTION – High-affinity histamine H_3 receptor agonist (pK_i = 7.9 against [3H]-(*R*)- α -methylhistamine binding in rat cerebral cortex) whose agonist activity was demonstrated in the [3S]-GTP γ S assay in rat brain preparations.

SOURCE – University of Kuopio, Kuopio (FI).

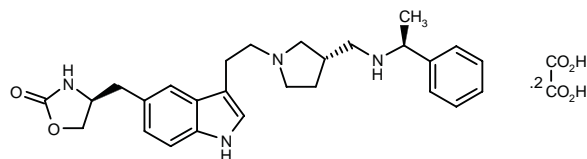
REFERENCES

1. Kovalainen, J.T. et al. *Investigation of the stereospecificity of the histamine H_3 -receptor with a series of new enantiomeric ligands*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.34.

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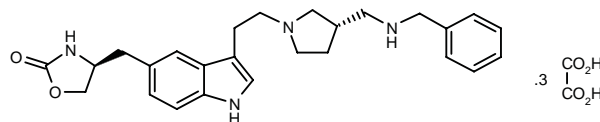
277065

4(*S*)-[3-[2-[3(*S*)-[1(*S*)-Phenylethylaminomethyl]-pyrrolidinyl]ethyl]-1*H*-indol-5-ylmethyl]oxazolidin-2-one dioxalate



C27 H34 N4 O2 . 2 C2 H2 O4; Mol wt: 626.6592

ACTION – Potent and selective human 5-HT $_{1D}$ receptor agonist (IC_{50} = 0.30 nM) with moderate to high selectivity over 5-HT $_{1A}$, 5-HT $_{1B}$ and 5-HT $_{2A}$ receptors (IC_{50} = 8.7, 49 and 2200 nM, respectively). In *in vitro* functional studies, compound showed full agonist activity, stimulating [3S]-GTP γ S binding to 5-HT $_{1D}$ receptors in CHO cells (EC_{50} = 0.5 nM; 98% efficacy). Potentially useful as a pharmacological tool to elucidate the role of 5-HT $_{1D}$ receptors in migraine. Another related compound is:



277063: C26 H32 N4 O2 . 3 C2 H2 O4

SOURCE – Merck Sharp & Dohme.

REFERENCES

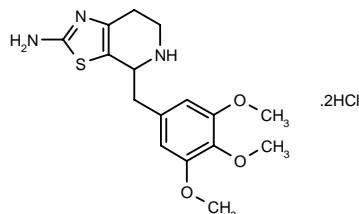
1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Azetidine, pyrrolidine and piperidine derivs. as 5HT $_1$ receptor agonists*. EP 796258, JP 98509721, WO 9617842.

2. Chen, C.-Y. and Larsen, R.D. (Merck & Co., Inc.) *Palladium catalyzed indolization*. US 5808064, WO 9806725.

3. Sternfeld, F. et al. *Synthesis and serotonergic activity of 3-[2-(pyrrolidin-1-yl)ethyl]indoles: Potent agonists for the h5-HT $_{1D}$ receptor with high selectivity over the h5-HT $_{1B}$ receptor*. J Med Chem 1999, 42(4): 677.

277703

4-(3,4,5-Trimethoxybenzyl)-4,5,6,7-tetrahydrothiazolo-[5,4-*c*]pyridin-2-amine dihydrochloride



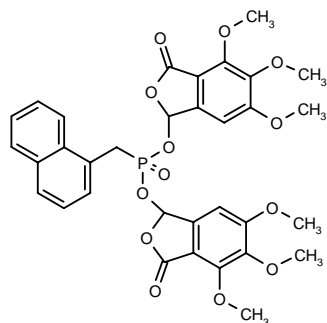
C16 H21 N3 O3 S . 2HCl; Mol wt: 408.3477

Pale yellow powder, m.p. 230-1 °C (decomp.).

DRUG DELIVERY

277388

(1-Naphthyl)methylphosphonic acid 4,5,6-trimethoxy-3-oxo-1,3-dihydrobenzofuran-1-yl diester



C33 H31 O13 P; Mol wt: 666.5689

ACTION – A 3-phthalidyl ester prodrug of 1-naphthalene-methylphosphonate (NMPA) with improved plasma half-life ($t_{1/2}$ = 5 min), plasma stability and safety (it does not generate formaldehyde) over traditional acycloxymethyl prodrugs.

SOURCE – Metabasis.

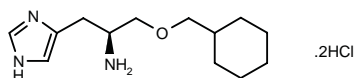
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PHARMACOLOGICAL TOOLS

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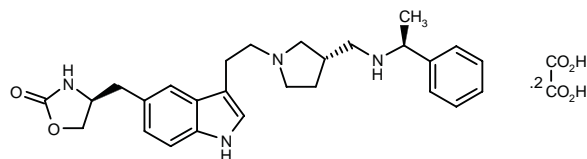
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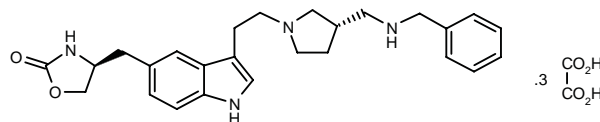
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C27 H34 N4 O2 . 2 C2 H2 O4; Mol wt: 626.6592

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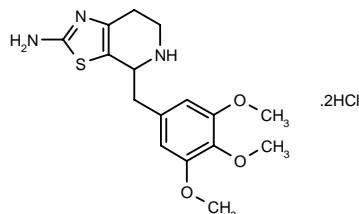
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277703

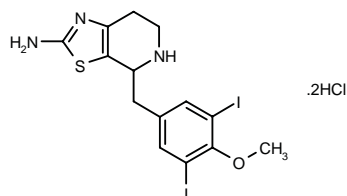
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C16 H21 N3 O3 S . 2HCl; Mol wt: 408.3477

Pale yellow powder, m.p. 230-1 °C (decomp.).

ACTION – Potent and selective human β_3 -adrenoceptor agonist ($pK_i = 4.17$) with high selectivity for β_3 - over β_1 - and β_2 -adrenoceptors, as demonstrated in functional assays in CHO cells, where it activated only β_3 -adrenoceptors and was inactive at β_1 - and β_2 -adrenoceptors. Potentially useful as a tool to elucidate the physiological role of β_3 -adrenoceptors and for designing compounds with potential for the treatment of obesity, type II diabetes and intestinal hypermotility disorders. Another related compound is:



277704: C₁₄ H₁₅ I₂ N₃ O S . 2HCl

SOURCE – Molecular Design International.

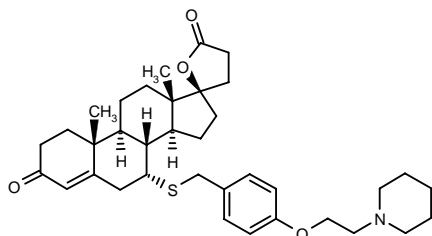
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2. Zheng, W. et al. 2-Amino-4-benzyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridines: Novel selective β_3 -adrenoceptor agonists. J Med Chem 1999, 42(12): 2287.

278089

7 α -[4-[2-(1-Piperidinyl)ethoxy]benzylsulfanyl]-17 α -3-oxopregn-4-ene-21,17-carbolactone



C₃₆ H₄₉ N O₄ S; Mol wt: 591.8521

ACTION – Potent and selective inhibitor of type II 17 β -hydroxysteroid dehydrogenase (17 β -HSD; $IC_{50} = 0.7 \mu M$) with no affinity (up to 10 μM) for steroid receptors including androgen, progestin, glucocorticoid and estrogen receptors. Potentially useful as a pharmacological tool to investigate the physiological role of this enzyme in biological systems.

SOURCE – Laval University, Quebec (CA).

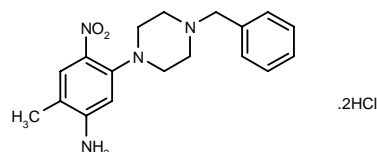
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1. Tremblay, M.R. et al. Spironolactone-related inhibitors of type II 17 β -hydroxysteroid dehydrogenase: Chemical synthesis, receptor binding affinities, and proliferative/antiproliferative activities. Bioorg Med Chem 1999, 7(6): 1013.

EGIS-7625*

259047

5-(4-Benzylpiperazin-1-yl)-2-methyl-4-nitroaniline dihydrochloride



C₁₈ H₂₂ N₄ O₂ . 2HCl; Mol wt: 399.3196

ACTION – Potent, selective and competitive 5-HT_{2B} receptor antagonist ($pA_2 = 9.4$ and 9.5, respectively, in rat stomach fundus and rabbit jugular vein) with high functional selectivity over 5-HT_{2A} receptors ($pA_2 = 6.7$ in rat pulmonary artery) and weak binding affinity for both 5-HT_{2A} and 5-HT_{2C} receptors ($pK_i = 6.5$ and 7.0, respectively, in rat frontal cortex and pig brain choroid plexus); compared to methysergide, a nonselective 5-HT₂ receptor antagonist, compound showed stronger activity and higher selectivity for 5-HT_{2B} receptors. Potentially useful as a pharmacological tool in serotonin research.

SOURCE – Egis.

REFERENCES

1. Rátzné Simonek, I. et al. (Egis Pharmaceuticals Ltd.) Novel piperazine or homopiperazine derivs., pharmaceutical compsns. containing the same and a process for their preparation. WO 9744334.

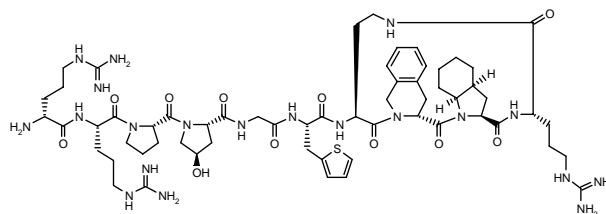
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*Identified compound **259047** Drug Data Report 1998, 020(03): 0200.

MEN-11270

277471

D-Arginyl-L-arginyl-L-prolyl-[4(R)-hydroxy]-L-prolyl-glycyl-3-(2-thienyl)-L-alanyl-L-(2,4-diaminobutyl)-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L-[(3a S, 7a S)-octahydroindol-2-ylcarbonyl]-L-arginine N-4.7-C-1.10-lactam



C₆₀ H₉₀ N₂₀ O₁₁ S; Mol wt: 1299.5660

ACTION – Potent peptide human bradykinin B₂ receptor antagonist with subnanomolar affinity for the B₂ receptor (pK_i = 10.3 in W138 fibroblast membranes) and high selectivity relative to B₁ receptors (pK_i = 6.0); it shows no relevant binding affinity (pIC₅₀ < 5.5) for a number of other receptors and ion channels. In functional studies on isolated human umbilical vein, compound showed a surmountable antagonism against bradykinin-induced contractions (pA₂ = 8.14) and did not modify the contractions induced by norepinephrine or 5-HT. A potential lead in the development of low-molecular-weight bradykinin antagonists as potential analgesic and antiinflammatory agents.

SOURCE – Menarini.

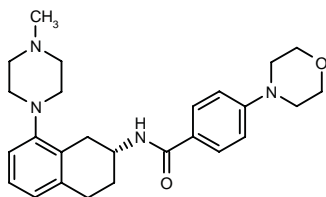
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NAS-438

277836

N-[8-(4-Methyl-1-piperazinyl)-1,2,3,4-tetrahydro-2(*R*)-naphthyl]-4-(4-morpholinyl)benzamide



C26 H34 N4 O2; Mol wt: 434.5806

ACTION – 5-HT_{1B/1D} receptor antagonist, as shown in functional assays by pD₂ values of 7.0 and 6.3, respectively, against 5-HT-induced vasoconstriction in dog basilar artery and saphenous vein, and pD₂ values of 7.0 and 6.00, respectively, against sumatriptan-induced vasoconstriction in dog basilar artery and saphenous vein. Potentially useful as a pharmacological tool for elucidating the functional role of these receptors.

SOURCE – AstraZeneca.

REFERENCES

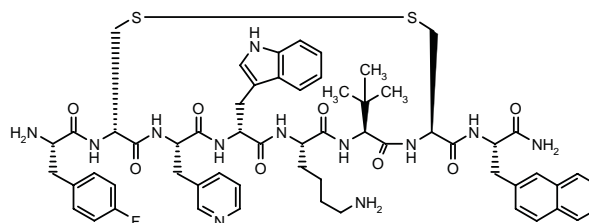
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2. Al. Saffar, A. et al. *The effects of a 5-HT_{1B/1D} receptor ligand on the isolated dog basilar artery and saphenous vein*. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PT95.

PRL-2903

277373

(4-Fluoro)-L-phenylalanyl-D-cysteinyl-(3-pyridyl)-L-alanyl-D-tryptophyl-L-lysyl-(3-methyl)-L-valyl-L-cysteinyl-(2-naphthyl)-L-alaninamide cyclic (2-7)-disulfide

DC-41-33



C59 H71 F N12 O8 S2; Mol wt: 1159.4160

ACTION – Potent and selective human somatostatin sst₂ receptor antagonist with high affinity for human sst₂ receptors (K_i = 26 nM) and good to high selectivity over hsst₃ and hsst₅ receptors (K_i = 231 and 535 nM, respectively) and no activity at hsst₁ and hsst₄ receptors (K_i > 1000 nM). In a functional assay in rat pituitary cells, compound antagonized the somatostatin-induced inhibition of growth hormone release with an IC₅₀ of 2.5 nM. In rats, when infused i.v. (50-1000 nmol/kg/h) it dose-dependently stimulated both basal glucagon and insulin secretion (ED₅₀ = 30 nmol/kg and 0.54 μmol/kg, respectively), and it was also able to completely reverse the effects of exogenous somatostatin such as the inhibition of glucagon secretion, inhibition of glucose-stimulated insulin secretion and inhibition of PACAP-27-stimulated insulin secretion. In conscious rats with chronic gastric fistula, i.v. infusion of compound dose-dependently antagonized somatostatin-induced inhibition of gastric acid secretion stimulated by pentagastrin (IC₅₀ = 31.6 nmol/kg/h) and completely reversed the effect of the glucose-dependent insulinotropic polypeptides GIP and GIP-(1-30)NH₂ and the glucagon-like polypeptide GLP-1(17-36)NH₂ on pentagastrin-stimulated gastric acid secretion. Potentially useful as a pharmacological tool to elucidate the physiological role of somatostatin and its receptor subtypes.

SOURCES – Biomeasure; Tulane University, New Orleans, LA (US).

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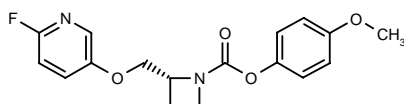
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2. Hocart, S.J. et al. *Highly potent cyclic disulfide antagonists of somatostatin*. J Med Chem 1999, 42(11): 1863.
3. Rossowski, W.J. et al. *Blockade of endogenous somatostatin employing a potent somatostatin antagonist confirms its profound role in mediating insulin and glucagon, additionally, leptin secretion*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P1-395.

ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

278340

2(R)-(6-Fluoropyridin-3-yloxymethyl)azetidine-1-carboxylic acid 4-methoxyphenyl ester



C17 H17 F N2 O4; Mol wt: 332.3293

ACTION – Prodrug of a potent and selective neuronal nicotinic acetylcholine (nACh) receptor ligand with potential in the treatment of pain, dementia, attention deficit disorder, anxiety associated with cognitive impairment, as well as withdrawal from substances of abuse. Parent compound exhibited a K_i value of 0.066 nM when tested *in vitro* for its ability to bind to nAChRs in crude synaptic membrane preparations from whole rat brain using [3 H]-cytisine as the radioligand, and it was also shown to interact with nAChRs in human neuroblastoma IMR-32 cells, giving an EC_{50} value of 1.1 μ M. Compound exhibited an oral bioavailability in terms of parent compound release of 37.7% in dogs. *In vivo*, it was shown to produce analgesia in the paw thermal stimulation model in rats at a dose of 0.62 μ mol/kg i.p. A representative compound from a series of heterocyclic ether and thioether compounds.

SOURCE – Abbott.

REFERENCES

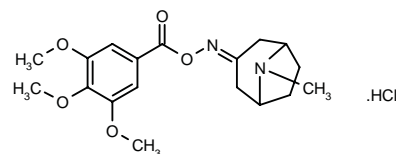
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ANTIMIGRAINE DRUGS

TROPOXIN

278376

8-Methyl-8-azabicyclo[3.2.1]octan-3-one O-(3,4,5-trimethoxybenzoyl)oxime hydrochloride



C18 H24 N2 O5 . HCl; Mol wt: 384.8575

ACTION – Potential antimigraine agent, a 5-HT₂ receptor antagonist (K_i = 0.11 μ M) reported to prevent the development of cerebrovascular constrictor responses induced by 5-HT both *in vitro* and *in vivo*. Compound showed functional 5-HT₂-antagonist activity by inhibiting the excitatory neuronal response to 5-HT at cortical 5-HT₂ receptors, and it inhibited the pressor response and sympathetic nerve discharge induced by stimulation of afferent tibial nerve fibers. It was also shown to protect against local ischemic brain injury induced by middle cerebral artery occlusion in rats, with an efficacy greater than that of methysergide and comparable to that of dihydroergotamine.

SOURCE – Russian Academy of Medical Sciences, Moscow (RU).

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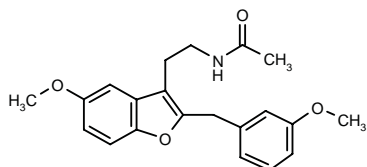
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2. Mirzoyan, R.S. et al. *Tropoxin - Novel 5HT2 receptor antagonist as a promising drug for migraine treatment*. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PT82.
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

278339

N-[2-[5-Methoxy-2-(3-methoxybenzyl)-1-benzofuran-3-yl]ethyl]acetamide



C₂₁ H₂₃ N O₄; Mol wt: 353.4157

ACTION – Agent with strong affinity for melatonin receptors particularly useful for the treatment of seasonal depression, sleep disorders, cardiovascular disorders, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic and antiarrhythmic activity, and to have a powerful effect on circadian rhythms via the melatonergic system in animal models.

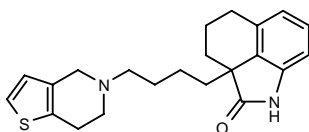
SOURCE – ADIR.

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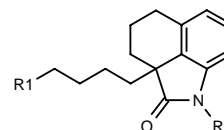
279315

2a-[4-(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-5-yl)butyl]-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indol-2-one



C₂₂ H₂₆ N₂ O S; Mol wt: 366.5264

ACTION – Agent for the treatment of CNS disorders with high affinity for 5-HT₇ receptors ($K_i = 0.9$ nM against [³H]-5-CT binding to cloned human 5-HT₇ receptors) and high selectivity over 5-HT₂ receptors ($K_i > 1000$ nM against [³H]-ketanserin binding in rat cortical preparations). Within this series of tetrahydrobenzo[*cd*]indole derivatives, the following are also included:



Compound	R1	R2	Formula
279316	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl	H	C ₂₆ H ₂₉ N ₃ O
279317	9-(CO ₂ Me)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl	H	C ₂₈ H ₃₁ N ₃ O ₃
279318	9-(MeOCH ₂)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl	H	C ₂₈ H ₃₃ N ₃ O ₂
279319	6-oxo-1,2,3,4,4a,5-hexahydro-pyrazino[2,1-c][1,4]benzothiazin-3-yl	H	C ₂₆ H ₃₁ N ₃ O ₂ S
279320	1,2,3,4-tetrahydro-2-isoquinoliny	Me	C ₂₅ H ₃₀ N ₂ O
279321	4-(1,2,3,4-tetrahydro-1-Naph)-1-Piz	H	C ₂₉ H ₃₇ N ₃ O
279322	4-(5,6,7,8-tetrahydro-5-isoquinoliny)-1-Piz	H	C ₂₈ H ₃₆ N ₄ O
279323	4-[PhCH(Me)]-1-Piz	H	C ₂₇ H ₃₅ N ₃ O

Agents acting on this receptor may be useful for the treatment of CNS disorders such as sleep disorders, anxiety, depression and schizophrenia.

SOURCE – Meiji Seika.

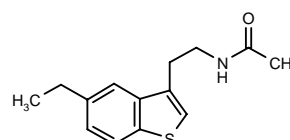
REFERENCES

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S-22153*

239187

N-[2-(5-Ethyl-1-benzothiophen-3-yl)ethyl]acetamide



C₁₄ H₁₇ N O S; Mol wt: 247.3603

ACTION – Melatonin receptor ligand with high affinity and selectivity for human mt₁ and MT₂ receptors ($pK_i = 8.7$ and 8.4 , respectively) relative to a large number of other receptors. In isolated rat tail arteries, compound antagonized melatonin-potentiated electrically evoked contractions ($pK_B = 7$). In mice, pretreatment with compound (10 or 20 mg/kg p.o.) was able to antagonize the melatonin-induced phase advances in a model of circadian rhythm disorders and the melatonin-induced neophobia in a free-exploratory test, whereas it had no effects by itself. Potentially useful both as a pharmacological tool for studying the physiological role of melatonin and for the treatment of circadian rhythm disorders

SOURCE – Servier.

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2. Delagrange, P. et al. *In vitro and in vivo antagonist properties of S 22153, a new melatonin ligand*. *Fundam Clin Pharmacol* 1999, 13(2): 253.

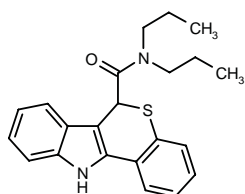
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*Identified compound **239187** Drug Data Rep 1996, 018(11): 0957.

ANXIOLYTICS

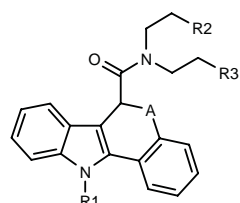
278488

N,N-Dipropyl-6,11-dihydro-1-benzothiopyrano[4,3-*b*]-indole-6-carboxamide



C22 H24 N2 O S; Mol wt: 364.5106

ACTION – Anxiolytic agent and antidepressant with high affinity for the mitochondrial diazepam binding inhibitor receptor (MDR; $IC_{50} = 0.368$ nM). A representative compound from a series of nitrogen-containing tetracyclic derivatives, wherein the following are also included:



Compound	R1	R2	R3	A	Formula
278489	H	H	H	S	C ₂₀ H ₂₀ N ₂ OS
278490	H	Bu	OPr	S	C ₂₇ H ₃₄ N ₂ O ₂ S
278491	Me	Bu	Bu	S	C ₂₉ H ₃₈ N ₂ OS
278492	H	Me	Me	SO ₂	C ₂₂ H ₂₄ N ₂ O ₃ S
278493	H	Bu	Bu	SO ₂	C ₂₈ H ₃₈ N ₂ O ₃ S
278494	H	Bu	Bu	CH ₂	C ₂₉ H ₃₈ N ₂ O

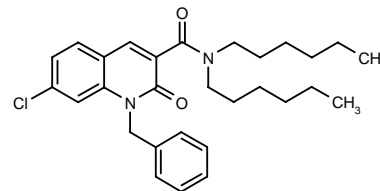
SOURCES – Nihon Nohyaku; Taisho.

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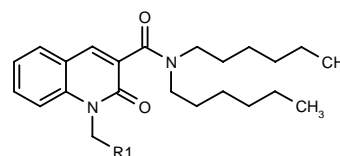
278495

1-Benzyl-7-chloro-*N,N*-dihexyl-2-oxo-1,2-dihydroquinoline-3-carboxamide



C29 H37 Cl N2 O2; Mol wt: 481.0763

ACTION – Anxiolytic agent and antidepressant with high affinity for the mitochondrial diazepam binding inhibitor receptor (MDR; $IC_{50} = 0.132$ nM). A representative compound from a series of 1,2-dihydro-2-oxoquinoline derivatives, wherein the following are also included:



Compound	R1	Formula
278496	Ph	C ₂₉ H ₃₈ N ₂ O ₂
278498	2-Pyr	C ₂₈ H ₃₇ N ₃ O ₂
278499	3-Pyr	C ₂₈ H ₃₇ N ₃ O ₂
278500	4-Pyr	C ₂₈ H ₃₇ N ₃ O ₂

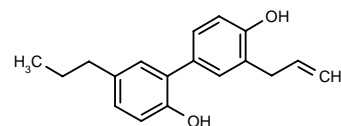
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

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279431

3'-Allyl-5-propylbiphenyl-2,4'-diol



C18 H20 O2; Mol wt: 268.3540

ACTION – Anxiolytic agent, a derivative of honokiol whose activity was demonstrated in the elevated plus-maze test in mice, where at a dose of 0.2 mg/kg p.o. it significantly increased time spent in open arms, being comparable in potency to diazepam at 1.0 mg/kg p.o. and more potent than honokiol at 20 mg/kg p.o.; coadministration of compound at 1 mg/kg p.o. with diazepam at 1 mg/kg resulted in significantly increased anxiolytic efficacy as compared to either drug alone. Contrary to honokiol, it did not prolong hexobarbital-induced sleeping time in mice. In addition, contrary to diazepam at 1 mg/kg p.o., compound was shown to be devoid of muscle relaxant effects in mice at 0.2-2.0 mg/kg p.o.

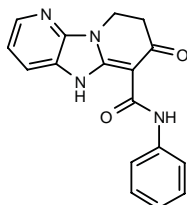
SOURCE – Tsumura.

REFERENCES

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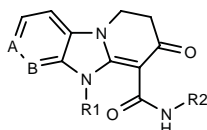
279839

7-Oxo-*N*-phenyl-5,7,8,9-tetrahydrodipyrdo[1,2-*a*:3',2'-*d*]-imidazole-6-carboxamide

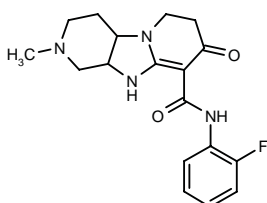


C17 H14 N4 O2; Mol wt: 306.3236

ACTION – Highly selective ligand for brain GABA_A receptors that interacts with the benzodiazepine binding site, expected to be useful in the treatment of anxiety, Down's syndrome, depression, sleep, cognitive and seizure disorders, overdose with benzodiazepine drugs and for enhancing alertness. Other exemplified oxo-dipyrdoimidazole-carboxamides include the following:



Compound	R1	R2	A	B	Formula
279840	H	CH2Ph	N	CH	C ₁₈ H ₁₆ N ₄ O ₂
279841	H	cyclohexyl-CH2	N	CH	C ₁₈ H ₂₂ N ₄ O ₂
279842	H	1,3-benzodioxol-4-yl-CH2	N	CH	C ₁₉ H ₁₆ N ₄ O ₄
279843	H	4-Ph-CH(Me)	N	CH	C ₁₉ H ₁₇ N ₄ O ₂
279844	H	5-MeO-2-Pyr	N	CH	C ₁₇ H ₁₅ N ₃ O ₃
279845	H	4-(1-imidazolyl-CH2)-PhCH2	N	CH	C ₂₂ H ₂₀ N ₆ O ₂
279846	H	1-Naph	N	CH	C ₂₁ H ₁₆ N ₄ O ₂
279849	Me	2-F-PhCH2	N	CH	C ₁₉ H ₁₇ N ₄ O ₂
279850	H	2-F-5-[N(Me)2CH2]-Ph	CH	N	C ₂₀ H ₂₀ N ₅ O ₂
279851	H	2-F-5-(4-morpholinyl-CH2CH2OCH2)-Ph	CH	N	C ₂₄ H ₂₆ N ₅ O ₄
279852	H	4-(i-BuNHCH2CH2O)-Ph	CH	N	C ₂₃ H ₂₇ N ₅ O ₃
279853	H	6-(BuNHCH2CH2O)-3-Pyr	CH	N	C ₂₂ H ₂₆ N ₆ O ₃
279854	CH2CH2-NHEt	2-F-Ph	CH	N	C ₂₁ H ₂₂ N ₅ O ₂
279855	Et	2-F-4-(1-pyrrolidinyl-CH2CH2O)-PhCH2	CH	N	C ₂₆ H ₃₀ N ₅ O ₃
279856	H	6-(BuNHCH2CH2O)-3-Pyr	N	CH	C ₂₂ H ₂₆ N ₆ O ₃



279847: C₁₈ H₂₁ F N₄ O₂

SOURCE – Neurogen.

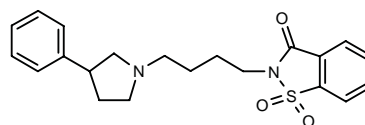
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LB-50016*

277032

2-[4-(3-Phenylpyrrolidin-1-yl)butyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide



C₂₁ H₂₄ N₂ O₃ S; Mol wt: 384.4976

ACTION – Potent 5-HT_{1A} receptor agonist (K_i = 2.7 nM) with relatively moderate affinity for 5-HT_{2A} receptors, α_2 -adrenoceptors and dopamine D₂ receptors (K_i = 34, 16 and 195 nM, respectively) and high selectivity over dopamine D₂ and muscarinic M₁ and M₂ receptors (K_i = 12,502, 857 and 706 nM, respectively). Compound exhibited *in vivo* properties indicating 5-HT_{1A} activation, i.e., elevation in serum corticosterone levels and induction of hypothermia in rats. In the mouse forced swimming test for antidepressant activity, compound dose-dependently reduced the immobility time with an ED₅₀ of 3 mg/kg i.p. The anxiolytic-like activity of LB-50016 was demonstrated in both the mouse face-to-face test, where it increased face-to-face interaction with an ED₅₀ of approximately 2 mg/kg i.p., and in the isolation-induced aggression test (3 mg/kg i.p.). Potentially useful for the treatment of anxiety and depression.

SOURCE – LG Chem.

REFERENCES

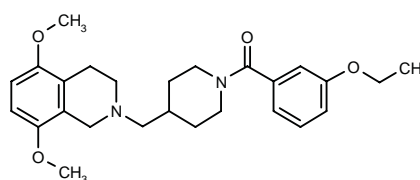
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*Identified compound **277032** Drug Data Rep 1999, 021(07): 0580.

SL-88.0338

269603

2-[1-(3-Ethoxybenzoyl)piperidin-4-ylmethyl]-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline



C₂₆ H₃₄ N₂ O₄; Mol wt: 438.5646

ACTION – Potent and selective 5-HT_{1A} receptor ligand ($K_i = 2.6$ nM in rat hippocampus) with more than 100-fold selectivity over 5-HT_{2A} and other neurotransmitter receptors. Compound showed functional antagonist activity in both *in vitro* and *in vivo* models of presynaptic and postsynaptic activity, and it exhibited inverse agonist effects by inhibiting 5-HT_{1A} receptor-mediated [³⁵S]-GTPγS binding in membranes from CHO cells expressing human 5-HT_{1A} receptors. In animal models of emotional behavior such as the elevated plus-maze, Vogel conflict test and defensive behavior in mice, compound showed anxiolytic-like activity. Potentially useful for the treatment of anxiety- or stress-related disorders.

SOURCE – Sanofi-Synthelabo.

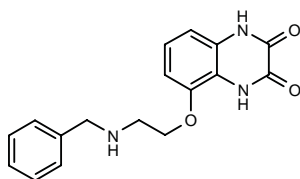
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- Green, R.D. et al. (R.P. Scherer Corp.) *Pharmaceutical compsn.* WO 9842344.
- Cohen, C. et al. *Pharmacological characterization of the selective 5-HT_{1A} receptor inverse agonist, SL88.0338-08*. Soc Neurosci Abstr 1998, 24(Part 2): Abstr 539.5.
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ANTIPSYCHOTIC DRUGS

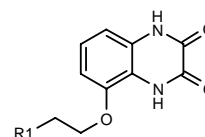
278468

5-[2-(Benzylamino)ethoxy]-1,2,3,4-tetrahydroquinoxaline-2,3-dione



C17 H17 N3 O3; Mol wt: 311.3393

ACTION – A selective dopamine autoreceptor agonist, as demonstrated in a binding assay in rat striatal brain tissue using [³H]-quinpirole as the ligand ($IC_{50} = 20.8$ nM), with relatively much lower affinity for postsynaptic dopamine D₂ receptors ($IC_{50} = 2187$ nM against [³H]-spiroperidol binding in limbic brain tissue). Potentially useful for the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome and alcohol or drug addiction. Other specifically claimed compounds from this series of 5-aminoalkoxy-1,4-dihydroquinoxaline-2,3-diones include the following:



Compound	R1	Formula
278469	4-Cl-PhCH ₂ NH	C ₁₇ H ₁₆ ClN ₃ O ₃
278470	1,2,3,4-tetrahydro-2-isoquinolinyl	C ₁₉ H ₁₉ N ₃ O ₃

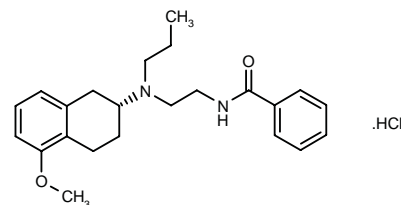
SOURCE – American Home Products.

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278716

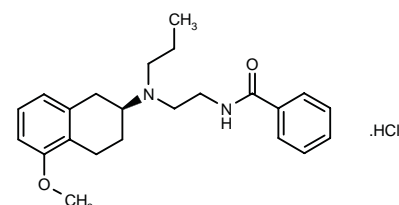
N-[2-[N-[5-Methoxy-1,2,3,4-tetrahydronaphthalen-2(R)-yl]-N-propylamino]ethyl]benzamide hydrochloride



C23 H30 N2 O2 . HCl; Mol wt: 402.9629

M.p. 91-3 °C.

ACTION – Potent dopamine D_{2A}, D₃ and 5-HT_{1A} receptor ligand ($K_i = 0.77$, 0.14 and 3.8 nM, respectively) with moderate affinity for α₁-adrenoceptors and 5-HT₂ receptors ($K_i = 124$ and 136 nM) and no affinity for α₂- and β-adrenoceptors, dopamine D₁ and muscarinic receptors ($K_i > 1000$ nM). The (*R*)-enantiomer of 5-OMe-BPAT, compound exhibited full agonist activity at the 5-HT_{1A} receptor, as demonstrated in GH₄ZD10 cells, where it inhibited vasoactive intestinal peptide (VIP)-induced cAMP production ($IC_{50} = 100$ nM, intrinsic efficacy = 100). *In vivo*, compound significantly inhibited the locomotor activity induced by *d*-amphetamine in rats ($EC_{50} = 2.6$ μmol/kg s.c.), indicating dopamine D₂ receptor antagonism, but did not induce catalepsy. Potentially useful as an atypical antipsychotic drug with a reduced liability for extrapyramidal side effects. The (**S**)-enantiomer exhibited a similar profile except that it enhanced the effect of *d*-amphetamine, suggesting dopamine D₂ receptor-stimulating effects.



278715: C23 H30 N2 O2 . HCl

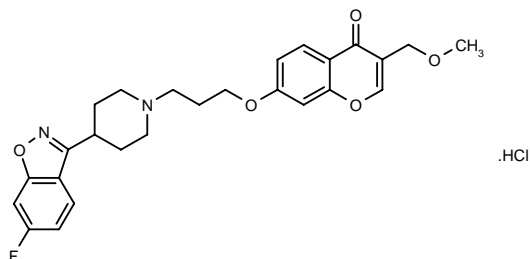
SOURCE – AstraZeneca.

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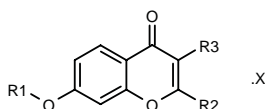
278844

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-3-(methoxymethyl)-1-benzopyran-4-one hydrochloride



C26 H27 F N2 O5 . HCl; Mol wt: 502.9672

ACTION – Agent for the treatment of psychosis, schizophrenia and allergy with high affinity for dopamine D₂, 5-HT_{2A} and histamine H₁ receptors (IC₅₀ = 0.339 nM against [³H]-pyrilamine binding in guinea pig cerebellum membranes). *In vivo*, compound inhibited apomorphine-induced climbing in mice with an ID₅₀ of 0.21 mg/kg p.o., being more potent than haloperidol (ID₅₀ = 0.32 mg/kg p.o.), while it induced catalepsy in rats only at much higher doses (ED₅₀ = 6.79 mg/kg p.o. vs. 2.00 mg/kg p.o. for haloperidol), indicating a reduced liability for inducing extrapyramidal side effects. Other exemplified compounds from this series of 7-[(piperidin-1-yl)propoxy]chromen-4-one derivatives include the following:



Compound	R1	R2	R3	X	Formula
278845	4-(6-F-1,2-benzisoxazol-3-yl)-1-Pip-(CH2)3	H	CHO		C ₂₅ H ₂₃ FN ₂ O ₅
278846	4-(6-F-1,2-benzisoxazol-3-yl)-1-Pip-(CH2)3	H	CO2H	HCl	C ₂₅ H ₂₃ FN ₂ O ₆ .HCl
278847	H	CH2OH	H		C ₁₀ H ₉ O ₄
278848	(CH2)3Cl	CH2OH	H		C ₁₃ H ₁₃ ClO ₄
278849	4-(6-F-1,2-benzisoxazol-3-yl)-1-Pip-(CH2)3	CH2OH	H	HCl	C ₂₅ H ₂₅ FN ₂ O ₅ .HCl

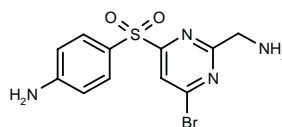
SOURCE – Ferrer.

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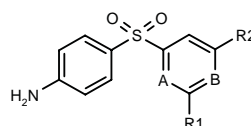
278963

4-[2-(Aminomethyl)-6-bromo-4-pyrimidinylsulfonyl]aniline



C11 H11 Br N4 O2 S; Mol wt: 343.2039

ACTION – Agent for the treatment or prevention of CNS disorders such as psychoses, schizophrenia, manic depression, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease with selective affinity for 5-HT₆ receptors. Other specifically claimed compounds within this series of benzosulfone derivatives include the following:



Compound	R1	R2	A	B	Formula
278964	Br	CH2NH2	N	CH	C ₁₂ H ₁₂ BrN ₃ O ₂ S
278965	OMe	OMe	CH	CH	C ₁₄ H ₁₅ NO ₄ S
279037	Br	CH2NH2	CH	N	C ₁₂ H ₁₂ BrN ₃ O ₂ S

SOURCE – Roche.

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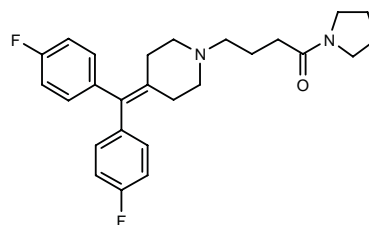
ORG-23366*

248199

4-[4-[Bis(4-fluorophenyl)methylene]piperidin-1-yl]-1-(1-pyrrolidinyl)-1-butanone

1-[4-[4-[Bis(4-fluorophenyl)methylene]-1-piperidinyl]-butyryl]pyrrolidine

Org-22110 (as monohydrochloride)



C26 H30 F2 N2 O; Mol wt: 424.5390

ACTION – Antipsychotic agent with high affinity for dopamine D₂ receptors (pK_i = 7.1), as well as for muscarinic M₁, 5-HT_{2A} and histamine H₁ receptors and α₁-adrenoceptors (pK_i = 6.9, 7.9, 7.6 and 7.3, respectively), with an *in vitro* binding profile similar to clozapine but improved D₂ affinity. *In vivo*, compound exhibited dopamine D₂ antagonism, as demonstrated by inhibition of apomorphine-induced climbing in mice (ED₅₀ = 0.5 mg/kg s.c., 2.8 mg/kg p.o.). The lack of cataleptogenic effect (ED₅₀ > 25 mg/kg in rats) at doses required for D₂ antagonism *in vivo* indicated a low liability for extrapyramidal side effects.

SOURCE – Akzo Nobel.

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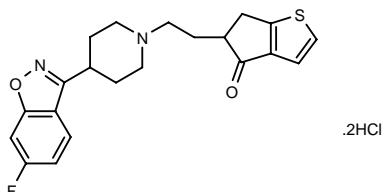
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*Identified compound **248199** Drug Data Rep 1997, 019(05): 0398.

QF-0510B²

278225

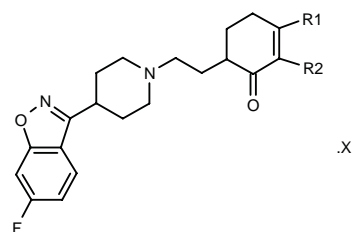
5-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-5,6-dihydro-4H-cyclopenta[b]thiophen-4-one dihydrochloride



C21 H21 F N2 O2 S . 2HCl; Mol wt: 457.3947

M.p. 230-2 °C.

ACTION – Atypical antipsychotic agent with good affinity for dopamine D₁ and D₂ receptors (pK_i = 6.90 and 7.70, respectively) and 5-HT_{2A} and 5-HT_{2C} receptors (IC₅₀ = 8.76 and 7.06, respectively), giving a favorable 5-HT₂/D₂ selectivity ratio of 1.14. *In vivo*, compound inhibited apomorphine-induced climbing in mice (ED₅₀ = 0.47 mg/kg i.p.) with greater potency than clozapine (ED₅₀ = 2.21 mg/kg i.p.) and lower potency than risperidone (ED₅₀ = 0.09 mg/kg i.p.), while being devoid of cataleptogenic effect. Moreover, compound (2 mg/kg i.p.) markedly inhibited spontaneous locomotor activity and amphetamine-induced hypermotility in mice with an effect greater than risperidone, reserpine, haloperidol and clozapine. Other representative compounds within this series of butyrophenones include the following:



Compound	R1,R2	X	Formula
QF-0610B [244571]	-SCH=CH-	HCl	C ₂₂ H ₂₃ FN ₂ O ₂ S.HCl
QF-0902B [278226] ²	-CH=CHS-	2HCl	C ₂₂ H ₂₃ FN ₂ O ₂ S.2HCl

SOURCES – Università di Bari, Bari (IT); Universitat Pompeu Fabra, Barcelona (ES); Universidad de Santiago de Compostela, Santiago de Compostela (ES).

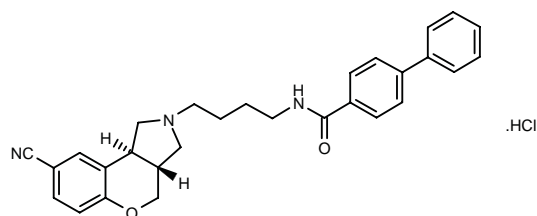
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S-33084

278866

N-[4-[(3a*R*,9b*S*)-8-Cyano-1,2,3,3a,4,9b-hexahydro-[1]benzopyrano[3,4-*c*]pyrrol-2-yl]butyl]biphenyl-4-carboxamide hydrochloride



C29 H29 N3 O2 . HCl; Mol wt: 488.0280

ACTION – Potent human dopamine D₃ receptor antagonist (pK_i = 9.5) with high selectivity over human D₂ receptors (pK_i = 7.5) and > 100-fold selectivity over human D₁, D₄ and D₅ receptors, as well as against a wide range of other receptors. Compound exhibited good brain penetration. Potentially useful as an antipsychotic agent.

SOURCE – Servier.

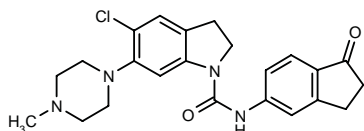
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TREATMENTS FOR MOOD DISORDERS

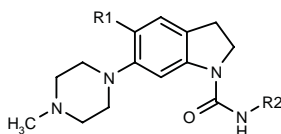
277730

5-Chloro-6-(4-methylpiperazin-1-yl)-*N*-(1-oxoindan-5-yl)-2,3-dihydro-1*H*-indole-1-carboxamide



C₂₃ H₂₅ Cl N₄ O₂; Mol wt: 424.9295

ACTION – Agent for the treatment of CNS disorders, particularly depression, with combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor-antagonist activity ($pK_i > 7.5$). Other specifically claimed compounds from this series of arylpiperazine and arylpiperidine derivatives include the following:



Compound	R1	R2	Formula
277731	Cl	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₄ H ₂₇ ClN ₄ O ₂
277732	Br	1-oxo-5-indanyl	C ₂₃ H ₂₅ BrN ₄ O ₂
277733	Br	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₄ H ₂₇ BrN ₄ O ₂
277735	Cl	9-oxo-2-fluorenyl	C ₂₇ H ₂₅ ClN ₄ O ₂
277736	Cl	9-oxo-3-fluorenyl	C ₂₇ H ₂₅ ClN ₄ O ₂
277737	OMe	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₅ H ₃₀ N ₄ O ₃
277738	OMe	5-oxo-5,6,7,8-tetrahydro-1-Naph	C ₂₅ H ₃₀ N ₄ O ₃

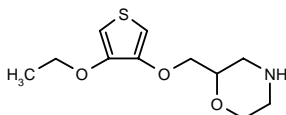
SOURCE – SmithKline Beecham.

REFERENCES

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278720

2-(4-Ethoxythien-3-yloxymethyl)morpholine



C₁₁ H₁₇ N O₃ S; Mol wt: 243.3253

M.p. 167-8 °C.

ACTION – Antidepressant, an analogue of viloxazine with strong activity in the forced swimming test, a murine model predictive of antidepressant properties (42% reduction in immobility at 25 mg/kg i.p.); it showed slight sedative action, induced slight hypothermia and potentiated pentobarbital sleeping time.

SOURCES – CSIC, Madrid (ES); Universidad de La Laguna, La Laguna (ES).

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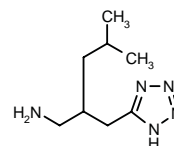
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

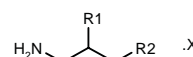
278005

4-Methyl-2-(1*H*-1,2,3,4-tetrazol-5-ylmethyl)pentylamine



C₈ H₁₇ N₅; Mol wt: 183.2573

ACTION – Anticonvulsant and neuronal injury inhibitor, also claimed for the treatment of depression, anxiety and panic. It was shown to bind to the calcium channel $\alpha 2\text{-}\delta$ subunit ($IC_{50} = 2.47 \mu M$ using [³H]-gabapentin as the radioligand and porcine brain tissue) and is expected to possess activity similar to gabapentin. Other specifically claimed compounds from this series of substituted amines include the following:



Compound	R1	R2	X	Formula
278006	i-Bu	5-thiooxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂	HCl	C ₉ H ₁₇ N ₃ OS .HCl
278007	i-Bu	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂	HCl	C ₉ H ₁₇ N ₃ O ₂ .HCl
278008	i-Bu	PO ₃ H ₂		C ₇ H ₁₅ NO ₃ P
278009	cyclopentyl	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂		C ₁₀ H ₁₇ N ₃ O ₂
278010	cyclopentyl	5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl-CH ₂		C ₁₀ H ₁₇ N ₃ OS
278011	cyclopentyl	2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl-CH ₂		C ₉ H ₁₇ N ₃ O ₂ S
278012	cyclobutyl	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂		C ₉ H ₁₅ N ₃ O ₂
278013	cyclobutyl	5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl-CH ₂		C ₉ H ₁₅ N ₃ OS
278014	cyclobutyl	2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl-CH ₂		C ₈ H ₁₅ N ₃ O ₂ S

SOURCE – Warner-Lambert.

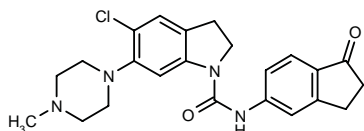
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TREATMENTS FOR MOOD DISORDERS

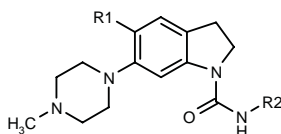
277730

5-Chloro-6-(4-methylpiperazin-1-yl)-*N*-(1-oxoindan-5-yl)-2,3-dihydro-1*H*-indole-1-carboxamide



C₂₃ H₂₅ Cl N₄ O₂; Mol wt: 424.9295

ACTION – Agent for the treatment of CNS disorders, particularly depression, with combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor-antagonist activity ($pK_i > 7.5$). Other specifically claimed compounds from this series of arylpiperazine and arylpiperidine derivatives include the following:



Compound	R1	R2	Formula
277731	Cl	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₄ H ₂₇ ClN ₄ O ₂
277732	Br	1-oxo-5-indanyl	C ₂₃ H ₂₅ BrN ₄ O ₂
277733	Br	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₄ H ₂₇ BrN ₄ O ₂
277735	Cl	9-oxo-2-fluorenyl	C ₂₇ H ₂₅ ClN ₄ O ₂
277736	Cl	9-oxo-3-fluorenyl	C ₂₇ H ₂₅ ClN ₄ O ₂
277737	OMe	5-oxo-5,6,7,8-tetrahydro-2-Naph	C ₂₅ H ₃₀ N ₄ O ₃
277738	OMe	5-oxo-5,6,7,8-tetrahydro-1-Naph	C ₂₅ H ₃₀ N ₄ O ₃

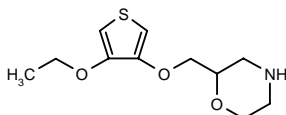
SOURCE – SmithKline Beecham.

REFERENCES

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278720

2-(4-Ethoxythien-3-yloxymethyl)morpholine



C₁₁ H₁₇ N O₃ S; Mol wt: 243.3253

M.p. 167-8 °C.

ACTION – Antidepressant, an analogue of viloxazine with strong activity in the forced swimming test, a murine model predictive of antidepressant properties (42% reduction in immobility at 25 mg/kg i.p.); it showed slight sedative action, induced slight hypothermia and potentiated pentobarbital sleeping time.

SOURCES – CSIC, Madrid (ES); Universidad de La Laguna, La Laguna (ES).

REFERENCES

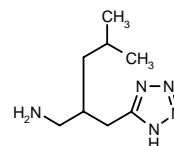
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

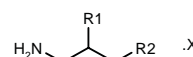
278005

4-Methyl-2-(1*H*-1,2,3,4-tetrazol-5-ylmethyl)pentylamine



C₈ H₁₇ N₅; Mol wt: 183.2573

ACTION – Anticonvulsant and neuronal injury inhibitor, also claimed for the treatment of depression, anxiety and panic. It was shown to bind to the calcium channel $\alpha_2\delta$ subunit ($IC_{50} = 2.47 \mu M$ using [³H]-gabapentin as the radioligand and porcine brain tissue) and is expected to possess activity similar to gabapentin. Other specifically claimed compounds from this series of substituted amines include the following:



Compound	R1	R2	X	Formula
278006	i-Bu	5-thiooxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂	HCl	C ₉ H ₁₇ N ₃ OS .HCl
278007	i-Bu	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂	HCl	C ₉ H ₁₇ N ₃ O ₂ .HCl
278008	i-Bu	PO ₃ H ₂		C ₇ H ₁₅ NO ₃ P
278009	cyclopentyl	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂		C ₁₀ H ₁₇ N ₃ O ₂
278010	cyclopentyl	5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl-CH ₂		C ₁₀ H ₁₇ N ₃ OS
278011	cyclopentyl	2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl-CH ₂		C ₉ H ₁₇ N ₃ O ₂ S
278012	cyclobutyl	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl-CH ₂		C ₉ H ₁₅ N ₃ O ₂
278013	cyclobutyl	5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl-CH ₂		C ₉ H ₁₅ N ₃ OS
278014	cyclobutyl	2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl-CH ₂		C ₈ H ₁₅ N ₃ O ₂ S

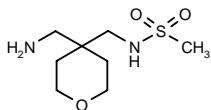
SOURCE – Warner-Lambert.

REFERENCES

1. Bryans, J.S. et al. (Warner-Lambert Co.) *Novel amines as pharmaceutical agents*. WO 9931074.

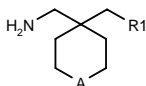
278015

N-[4-(Aminomethyl)tetrahydropyran-4-ylmethyl]methanesulfonamide



C8 H18 N2 O3 S; Mol wt: 222.3072

ACTION – An analogue of gabapentin reported to display good affinity for the Ca^{2+} receptor $\alpha 2\text{-}\delta$ binding site, with potential in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic disorders, pain, inflammation and gastrointestinal disorders. Other specifically claimed compounds from this series of 4(3)-substituted-4(3)-aminomethyl-(thio)pyran or -piperidine derivatives include the following:



Compound	R1	A	Formula
278016	NHSO ₂ CF ₃	O	C ₈ H ₁₅ F ₃ N ₂ O ₃ S
278017	NHCOCH ₂ Ph	S	C ₁₅ H ₂₂ N ₂ O ₂ S
278018	PO ₃ H ₂	SO ₂	C ₇ H ₁₆ NO ₅ PS
278019	5-thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	NH	C ₉ H ₁₆ N ₄ OS
278020	NH ₂	N(Me)	C ₁₆ H ₂₅ N ₃ O

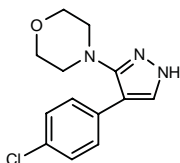
SOURCE – Warner-Lambert.

REFERENCES

1. Bryans, J.S. et al. (Warner-Lambert Co.) 4(3)Subst.-4(3)-aminomethyl-(thio)pyran or -piperidine derivs. (=gabapentin analogues), their preparation and their use in the treatment of neurological disorders. WO 9931057.

278252

4-[4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]morpholine



C13 H14 Cl N3 O; Mol wt: 263.7266

M.p. 185-8 °C.

ACTION – Anticonvulsant able to protect against maximal electroshock (MES) seizures in mice (ED_{50} = 47 mg/kg i.p.) at doses devoid of neurotoxicity in the rotarod test (> 100 mg/kg); it exhibited strong voltage-dependent sodium channel-blocking activity superior to the reference compound phenytoin.

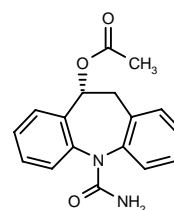
SOURCE – Asta Medica.

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1. Lankau, H.-J. et al. 3-Amino- and 5-aminopyrazoles with anticonvulsant activity. Arch Pharm 1999, 332(6): 219.
2. Liebscher, J. et al. Formylation products of thiomides. IV. Reactions of 3-(dialkylamino)- and 3-hydroxythioacrylamides with amines - Synthesis of 3-aminothioacrylamides, 5-aminopyrazoles and 3-aminoisothiazolium salts. J Prakt Chem 1983, 325(5): 689.
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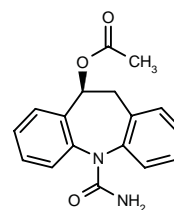
278669

Acetic acid 5-carbamoyl-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10(*R*)-yl ester



C17 H16 N2 O3; Mol wt: 296.3244

ACTION – Anticonvulsant proven to protect rats against maximal electroshock (MES) seizures (ED_{50} = 10.9 and 18 mg/kg given p.o. and i.p., respectively) with little motor impairment (ED_{50} > 1000 mg/kg p.o. and 134.9 mg/kg i.p. in the rat rotarod test). Compound exhibited sodium channel-blocking properties, as demonstrated in rat cortical synaptosomes by displacement of [³H]-batrachotoxin binding (IC_{50} = 113 nM) and by inhibition of ²²Na⁺ uptake. Another related 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide derivative is:



278670: C17 H16 N2 O3

SOURCE – Bial.

REFERENCES

1. Benes, J. and Vieira Araujo Soares da Silva, P.M. (Portela & Ca., SA) Substd. dihydrodibenzo[*b,f*]azepines, method of their preparation, their use in the treatment of some central nervous system disorders, and pharmaceutical compsns. containing them. EP 751129, US 5753646.
2. Benes, J. et al. Anticonvulsant and sodium channel-blocking properties of novel 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide derivatives. J Med Chem 1999, 42(14): 2587.

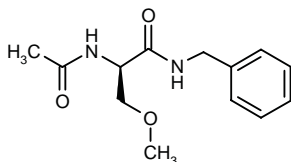
HARKOSERIDE

278582

2(*R*)-Acetamido-*N*-benzyl-3-methoxypropionamide

N-Acetyl-*O*-methyl-D-serine benzylamide

ADD-234037



C13 H18 N2 O3; Mol wt: 250.2962

M.p. 143-4 °C, $[\alpha]_D^{23} +16.0^\circ$ (*c* 1, MeOH).

ACTION – Anticonvulsant, an NMDA receptor glycine-site antagonist possessing protective activity against maximal electroshock (MES) seizures in mice (ED_{50} = 4.5 mg/kg i.p.) and rats (3.9 mg/kg p.o.) and low neurological toxicity (TD_{50} = 27 mg/kg i.p., > 500 mg/kg p.o. in the rotarod test in mice and rats, respectively). In a model of experimental status epilepticus in rats, compound showed protective activity against generalized tonic-clonic seizures (median effective dose [MED] = 45 mg/kg) and it enhanced the anticonvulsant efficacy of diazepam. In healthy volunteers, it showed a good safety profile, with no serious adverse effects, and a favorable pharmacokinetic profile.

SOURCE – Research Corporation Technologies.

REFERENCES

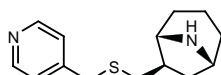
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- Franklin, M.R. *Comparative hepatic effects of two anticonvulsants, harkoseride and carbamazepine, in rat*. FASEB J 1999, 13(5, Part 2): Abst 630.9.
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- Harris FRC establishes safety of candidate antiepileptic drug in volunteer studies. DailyDrugNews.com (Daily Essentials) 1998, Dec 3.

COGNITION-ENHANCING DRUGS

278308

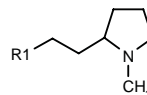
exo-6-(Pyridin-4-ylmethylsulfanylmethyl)-8-azabicyclo[3.2.1]octane

exo-(8-Azabicyclo[3.2.1]oct-6-ylmethyl)(4-pyridylmethyl)-sulfide

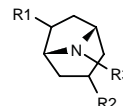


C14 H20 N2 S; Mol wt: 248.3920

ACTION – Agent for the treatment of Alzheimer's disease, Parkinson's disease, depression, anxiety, psychosis, substance abuse and neurocrine disorders that acts by modulating neuronal nicotinic acetylcholine (nACh) receptors, as demonstrated by modulation of calcium flux in a functional assay using the $\alpha 2\beta 4$ subtype. It is reported to potentiate neurotransmission by promoting the release of neurotransmitters such as acetylcholine, dopamine and norepinephrine. A representative compound from a series of substituted pyridine derivatives, wherein the following are also included:



Compound	R1	Isomer	Formula
278309	2-Pyr-S		C ₁₂ H ₁₈ N ₂ S
278310	4-Pyr-S		C ₁₂ H ₁₈ N ₂ S
278311	2-Pyr-CH2S		C ₁₃ H ₂₀ N ₂ S
278312	4-Pyr-CH2S		C ₁₃ H ₂₀ N ₂ S
278318	2-Pyr-O		C ₁₂ H ₁₈ N ₂ O
278319	4-Pyr-O		C ₁₂ H ₁₈ N ₂ O
278320	2-Pyr-S	R	C ₁₂ H ₁₈ N ₂ S
278321	2-Pyr-S	S	C ₁₂ H ₁₈ N ₂ S



Compound	R1	R2	R3	Isomer	Formula
278313	H	2-Pyr-S	Me	exo	C ₁₃ H ₁₈ N ₂ S
278314	H	2-Pyr-CH2S	Me	exo	C ₁₄ H ₂₀ N ₂ S
278315	2-Pyr-SCH2	H	H	endo	C ₁₃ H ₁₈ N ₂ S
278316	2-Pyr-SCH2	H	H	exo	C ₁₃ H ₁₈ N ₂ S
278317	4-Pyr-CH2SCH2	H	H	endo	C ₁₄ H ₂₀ N ₂ S

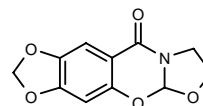
SOURCE – Sibia Neurosciences.

REFERENCES

- Vernier, J.-M. et al. (SIBIA Neurosciences, Inc.) *Novel subst. pyridine cpds. useful as modulators of acetylcholine receptors*. WO 9932117.

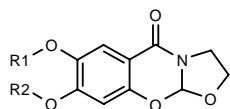
278737

7,8-Dihydro-5a*H*-1,3-dioxolo[4,5-*g*]oxazolo[2,3-*b*]-1,3-benzoxazin-10-one



C11 H9 N O5; Mol wt: 235.1941

ACTION – Agent that enhances synaptic responses mediated by AMPA receptors, potentially useful for the treatment of memory impairment or other cognitive disorders and schizophrenia. *In vitro* activity was demonstrated by a 34% increase in the amplitude of excitatory postsynaptic potentials (EPSPs) in rat hippocampus slices at 30 μ M. Its memory-enhancing activity was demonstrated *in vivo* in the 8-arm radial maze test in rats. Other specifically claimed compounds within this series of benzoxazine derivatives include the following:



Compound	R1	R2	Formula
278738		-CH ₂ CH ₂ -	C ₁₂ H ₉ NO ₅
278739		-C(Me) ₂ -	C ₁₃ H ₁₃ NO ₅

SOURCE – Cortex.

REFERENCES

1. Rogers, G.A. and Marrs, C. (Cortex Pharmaceuticals Inc.) *Benzoxazine cpds. for enhancing synaptic response*. WO 9933469.

AN-1792

278109

Human β -amyloid peptide (1-42)

Aspartyl-alanyl-glutamyl-phenylalanyl-arginyl-histidyl-aspartyl-seryl-glycyl-tyrosyl-glutamyl-valyl-histidyl-histidyl-glutaminyl-lysyl-leucyl-valyl-phenylalanyl-phenylalanyl-alanyl-glutamyl-aspartyl-valyl-glycyl-seryl-asparaginyl-lysyl-glycyl-alanyl-isoleucyl-isoleucyl-glycyl-leucyl-methionyl-valyl-glycyl-glycyl-valyl-valyl-isoleucyl-alanine

A β 42

C203 H311 N55 O60 S; Mol wt: 4514.0810

ACTION – Cognition-enhancing agent for the treatment of Alzheimer's disease, a 42-amino-acid form of the β -amyloid peptide. Transgenic (PDAPP) mice immunized with AN-1792 showed a significant reduction in preexisting amyloid plaque and inhibition of further plaque formation in the brain.

SOURCE – Elan.

REFERENCES

1. Schenk, D.B. (Athena Neurosciences, Inc.) *Prevention and treatment of amyloidogenic disease*. WO 9927944.

2. Schenk, D. et al. *Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse*. Nature 1999, 400(6740): 173.

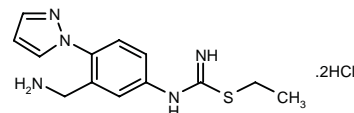
3. St George-Hyslop, P.H. and Westaway, D.A. *Antibody clears senile plaques*. Nature 1999, 400(6740): 116.

4. *Experimental therapy may be useful in treating and preventing Alzheimer's disease*. Elan Corp. Plc Press Release 1999, July 7.

TREATMENT OF CEREBROVASCULAR DISEASES

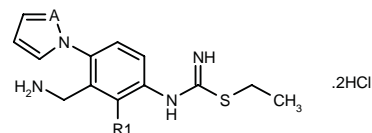
277496

*N*¹-[3-(Aminomethyl)-4-(1*H*-pyrazol-1-yl)phenyl]-*S*-ethyl-isothiourea dihydrochloride



C13 H17 N5 S . 2HCl; Mol wt: 348.3001

ACTION – Nitric oxide synthase (NOS) inhibitor that acts as a selective inhibitor of the neuronal isoform of the enzyme (nNOS) relative to the inducible (iNOS) and endothelial isoforms (eNOS). It showed an IC₅₀ value for nNOS prepared from rat cerebral cortex of 6.3 nM compared to values for eNOS prepared from bovine pulmonary arterial vascular endothelial cells and for iNOS of 5130 and 20,500 nM, respectively. Compound is thus expected to be useful for the treatment of cerebrovascular disorders. Other exemplified heterocyclic compounds include the following:



Compound	R1	A	Formula
277497	H	CH	C ₁₄ H ₁₈ N ₄ S.2HCl
277498	Me	N	C ₁₄ H ₁₉ N ₅ S.2HCl

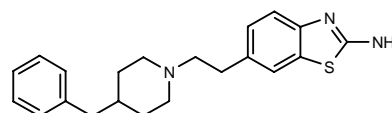
SOURCE – Chugai.

REFERENCES

1. Makino, T. (Chugai Pharmaceutical Co. Ltd.) *Heterocyclic cpds. having NOS inhibitory activity*. WO 9923069.

277540

6-[2-(4-Benzylpiperidin-1-yl)ethyl]benzothiazol-2-amine



C21 H25 N3 S; Mol wt: 351.5155

ACTION – Neuroprotective agent able to modulate or antagonize the neurotoxic effects of endogenous excitatory amino acids (EAAs) at the CNS level. It was more potent than eliprodil in increasing cell viability in rat mixed cortical neuronal cultures exposed to NMDA (EC_{50} = 0.64 μ M vs. 2.26 μ M). Potentially useful in the prevention and/or treatment of acute or chronic neurodegenerative disorders including ischemia, hypoglycemia, hypoxia, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, Tourette's syndrome and motor neuron disease.

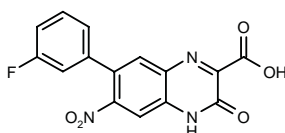
SOURCE – Pharmacia & Upjohn.

REFERENCES

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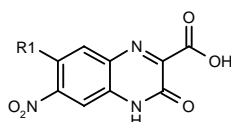
277614

7-(3-Fluorophenyl)-6-nitro-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid



C15 H8 F N3 O5; Mol wt: 329.2422

ACTION – AMPA receptor antagonist with good affinity for the receptor in a binding assay using [3 H]-AMPA as the radioligand and crude rat cerebral cortex synaptosomal membrane preparations (K_i = 0.40 μ M). Other exemplified 7-arylquinoxaline-carboxylate derivatives include the following:



Compound	R1	Formula
277616	Ph	C ₁₅ H ₉ N ₃ O ₅
277617	4-F-Ph	C ₁₅ H ₈ FN ₃ O ₅
277618	4-Br-Ph	C ₁₅ H ₈ BrN ₃ O ₅
277619	2-Naph	C ₁₈ H ₁₁ N ₃ O ₅
277620	3,4-(F)2-Ph	C ₁₅ H ₇ F ₂ N ₃ O ₅
277621	3,5-(F)2-Ph	C ₁₅ H ₇ F ₂ N ₃ O ₅

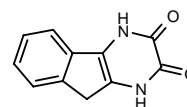
SOURCE – Kyorin.

REFERENCES

1. Takano, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *7-Arylquinoxaline carboxylate derivs. and their salts, and their preparation method.* JP 99130756.

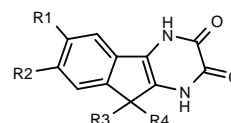
278601

2,3,4,9-Tetrahydro-1H-indeno[1,2-b]pyrazine-2,3-dione



C11 H8 N2 O2; Mol wt: 200.1962

ACTION – Cerebral antiischemic and neuroprotective agent, an AMPA receptor antagonist and noncompetitive glycine-site NMDA receptor antagonist with low toxicity (LD_{50} > 50 mg/kg i.p. in mice). Other specifically claimed compounds from this series of 1H-indeno[1,2-b]pyrazine-2,3-dione derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
278602	Cl	H	H	H		C ₁₁ H ₇ ClN ₂ O ₂
278603	H	H	Me	CH ₂ CO ₂ H		C ₁₄ H ₁₂ N ₂ O ₄
278604	Cl	H	H	NH ₂		C ₁₁ H ₈ ClN ₃ O ₂
278605	H	NHCONHPh	H	H		C ₁₈ H ₁₄ N ₄ O ₃
278606	Cl	H	-CH(CO ₂ H)-			C ₁₃ H ₇ ClN ₂ O ₄
278607	Cl	H	Me	CH ₂ CO ₂ H		C ₁₄ H ₁₁ ClN ₂ O ₄
278608	H	H	Me	CH ₂ CO ₂ H	(+)	C ₁₄ H ₁₂ N ₂ O ₄
278609	H	H	Me	CH ₂ CO ₂ H	(-)	C ₁₄ H ₁₂ N ₂ O ₄
278610	Cl	H	Me	CH ₂ CO ₂ H	(+)	C ₁₄ H ₁₁ ClN ₂ O ₄
278611	Cl	H	Me	CH ₂ CO ₂ H	(-)	C ₁₄ H ₁₁ ClN ₂ O ₄

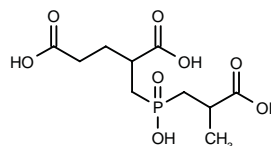
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Aloup, J.-C. et al. (Rhône-Poulenc Rorer SA) *5H-Indeno[1,2-b]pyrazine-2,3-dione derivs., their preparation and medicinal products containing them.* US 5922716, WO 9526342.

278624

2-[2-Carboxypropyl(hydroxy)phosphorylmethyl]glutaric acid



C10 H17 O8 P; Mol wt: 296.2103

ACTION – Agent for the treatment of glutamate abnormalities such as stroke, Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease, as well as prostate diseases, particularly prostate cancer, that acts by inhibiting *N*-acetylated α -linked acidic dipeptidase (NAALADase) activity (K_i = 1.5 nM). A representative compound from a series of phosphinic alkanic acid derivatives.

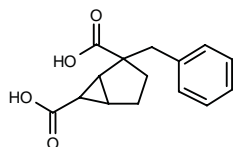
SOURCE – Guilford.

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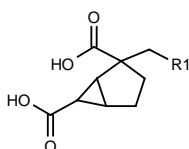
278771

2-Benzylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C₁₅ H₁₆ O₄; Mol wt: 260.2874

ACTION – Agent for the treatment of disorders characterized by inappropriate glutamate neurotransmission such as stroke, head trauma, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, urinary incontinence, psychosis, convulsions, anxiety, depression, emesis and chronic or acute pain, that acts as a selective modulator of class II metabotropic glutamate receptors. Other compounds from this series of bicyclo[3.1.0]hexane derivatives include the following:



Compound	R1	Formula
278773	4-Cl-Ph	C ₁₅ H ₁₅ ClO ₄
278775	3,4-(Cl) ₂ -Ph	C ₁₅ H ₁₄ Cl ₂ O ₄
278777	4-MeO-Ph	C ₁₆ H ₁₈ O ₅
278778	2-thienyl	C ₁₃ H ₁₄ O ₄ S
278780	4-N(Et) ₂ -Ph	C ₁₉ H ₂₅ NO ₄
278781	3-Pyr	C ₁₄ H ₁₅ NO ₄
278782	4-Pyr	C ₁₄ H ₁₅ NO ₄

SOURCE – Pfizer.

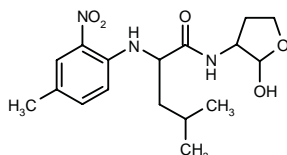
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279235

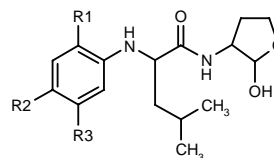
N-(2-Hydroxytetrahydrofuran-3-yl)-4-methyl-2-(4-methyl-2-nitrophenylamino)pentanamide

*N*¹-(2-Hydroxytetrahydrofuran-3-yl)-*N*²-(4-methyl-2-nitrophenyl)-DL-leucinamide



C₁₇ H₂₅ N₃ O₅; Mol wt: 351.4005

ACTION – A potent inhibitor of cysteine proteases such as calpain (IC₅₀ = 0.14 μM using enzyme purified from porcine kidney). Within this series of oxygen-containing heterocycles, the following are also included:



Compound	R1	R2	R3	Formula
279236	NO ₂	Cl	Cl	C ₁₆ H ₂₁ Cl ₂ N ₃ O ₅
279237	NO ₂	H	H	C ₁₆ H ₂₃ N ₃ O ₅
279238	NO ₂	F	H	C ₁₆ H ₂₂ FN ₃ O ₅
279239	Cl	NO ₂	H	C ₁₆ H ₂₂ ClN ₃ O ₅
279240	CF ₃	NO ₂	H	C ₁₇ H ₂₂ F ₃ N ₃ O ₅
279241	NO ₂	H	Cl	C ₁₆ H ₂₂ ClN ₃ O ₅
279242	F	NO ₂	H	C ₁₆ H ₂₂ FN ₃ O ₅

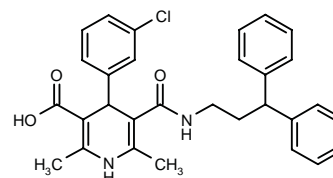
SOURCE – Mitsubishi Chemical.

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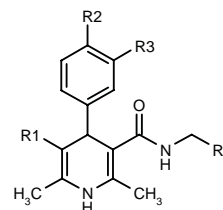
279256

4-(3-Chlorophenyl)-5-[*N*-(3,3-diphenylpropyl)carbamoyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylic acid



C₃₀ H₂₉ Cl N₂ O₃; Mol wt: 501.0231

ACTION – N-type calcium channel blocker (pIC₅₀ = 6.2 in human neuroblastoma IMR-32 cells), a representative compound from a series of 1,4-dihydropyridine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
279257	CO ₂ H	H	NO ₂	(E)-CH=CHPh	C ₂₄ H ₂₃ N ₃ O ₅
279258	CO ₂ H	H	CN	(E)-CH=CHPh	C ₂₅ H ₂₃ N ₃ O ₃
279259	CN	H	Cl	(E)-CH=CHPh	C ₂₄ H ₂₂ ClN ₃ O
279260	CO ₂ H	NO ₂	H	(E)-CH=CHPh	C ₂₄ H ₂₃ N ₃ O ₅
279261	CO ₂ H	H	Cl	CONHPh	C ₂₃ H ₂₃ ClN ₃ O ₄
279262	CO ₂ H	H	Cl	(E)-CH=CHPh	C ₂₄ H ₂₃ ClN ₂ O ₃

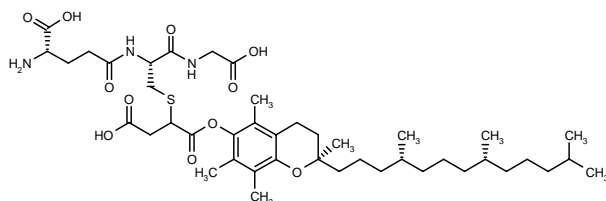
SOURCE – Ajinomoto.

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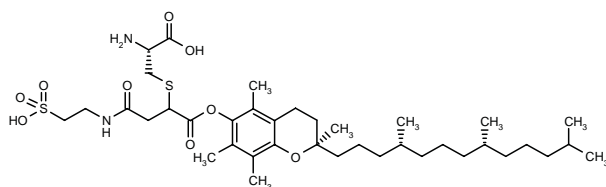
279460

S-[1-(Carboxymethyl)-2-oxo-2-[2(*R*),5,7,8-tetramethyl-2-[4(*R*),8(*R*),12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yloxy]ethyl]-*N*-(*L*-γ-glutamyl)-*L*-cysteinylglycine



C43 H69 N3 O11 S; Mol wt: 836.0941

ACTION – Vitamin E derivative with potential as a cerebral metabolism activator, hepatoprotectant, anticataract agent and antioxidant. *In vitro*, compound was shown to inhibit lipid peroxidation in rat brain homogenates, giving 85.64% inhibition at 10 μM. Another exemplified compound is:



279461: C38 H64 N2 O9 S2

SOURCE – Senju.

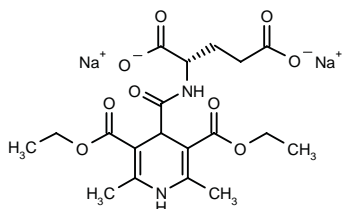
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GLUTAPYRONE*1,4-8,10-12

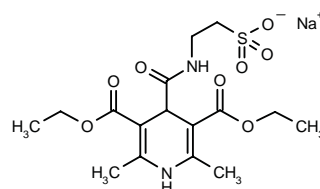
103223

4-[*N*-[1(*S*),3-Dicarboxypropyl]carbamoyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester disodium salt



C19 H24 N2 Na2 O9; Mol wt: 470.3836

ACTION – Neuroprotective agent able to protect cerebellar granule cell cultures from oxygen/glucose deprivation-induced cell death, as demonstrated by a decrease in lactate dehydrogenase release (55-79% at 1-100 μM); it may act by regulating cell energy metabolism. Another related dihydropyridine derivative is:



Tauropyrone [210025]2,3,6,9:** C16 H23 N2 Na O8 S

SOURCE – Latvian Institute of Organic Synthesis, Riga (LV).

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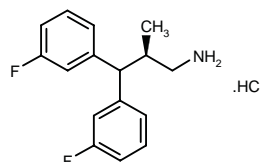
*Identified compound **103223** Drug Data Rep 1985, 007(05): 0286.

Identified compound **210025 Drug Data Rep 1994, 016(08): 0736.

NPS-1392

278856

(-)-3,3-Bis(3-fluorophenyl)-2(*R*)-methylpropan-1-amine hydrochloride



C16 H17 F2 N . HCl; Mol wt: 297.7742

M.p. 260-70 °C (*decomp.*).

ACTION – Neuroprotective agent, a potent NMDA receptor antagonist with an IC_{50} value of 75 nM for inhibition of NMDA/glycine-induced increases in cytosolic calcium in cultured rat cerebellar granule cells and an IC_{50} value of 141 nM for displacement of [3H]-MK-801 binding from NMDA receptors in rat cortex. Compound exhibited neuroprotective activity in a rat model of temporary focal ischemia, giving a 37% reduction in cerebral infarct volume after administration of 2 doses of 2 mg/kg i.p. 30 min prior to ischemia and 3 h after ischemia. Potentially useful for the treatment of ischemic stroke.

SOURCE – NPS Pharmaceuticals.

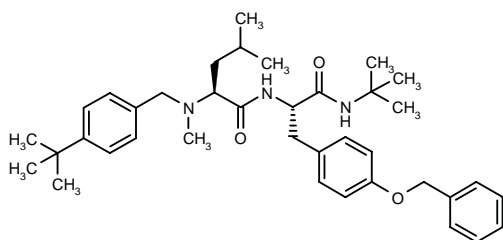
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PD-173212¹⁻⁵

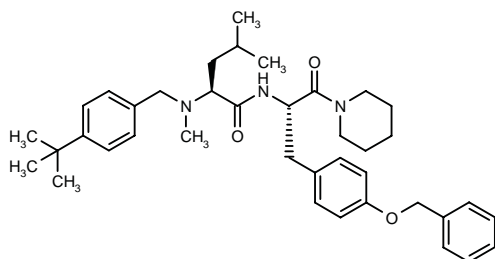
274082

N-(4-*tert*-Butylbenzyl)-*N*-methyl-L-leucyl-4-*O*-(benzyl)-L-tyrosine *tert*-butylamide



C38 H53 N3 O3; Mol wt: 599.8547

ACTION – Potent N-type calcium channel blocker (IC_{50} = 36 nM in the IMR-32 assay) with high selectivity over neuronal Na^+ , K^+ and L-type channels (IC_{50} > 10 μ M). Compound strongly blocked N-type calcium channel currents in whole-cell voltage-clamp experiments (IC_{50} = 74 nM) and showed efficacy in preventing tonic seizures in the audiogenic seizure model in mice (60% protection at 30 mg/kg i.v.). Potentially useful for the treatment of stroke or pain. Another specifically claimed compound is:



278079^{1,4}: C39 H53 N3 O3

SOURCES – Elan; Warner-Lambert.

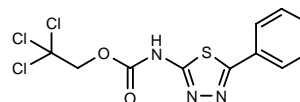
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PNU-153833

277528

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)carbamic acid 2,2,2-trichloroethyl ester



C11 H8 Cl3 N3 O2 S; Mol wt: 352.6282

ACTION – Kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor giving an IC_{50} for inhibition of enzyme from rat liver mitochondria of 0.8 μ M. It is expected to be useful in the treatment and/or prevention of neuropathological processes including Huntington's chorea, Alzheimer's disease, Parkinson's disease, other dementias, amyotrophic lateral sclerosis, cerebral ischemia and hypoxia, spinal and head trauma, and epilepsy.

SOURCE – Pharmacia & Upjohn.

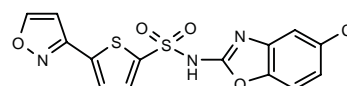
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PNU-191386

277529

N-(5-Chlorobenzoxazol-2-yl)-5-(isoxazol-3-yl)thiophene-2-sulfonamide



C14 H8 Cl N3 O4 S2; Mol wt: 381.8192

ACTION – Kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor ($IC_{50} = 10.4 \mu M$ for inhibition of rat liver mitochondrial enzyme) expected to be useful in the treatment and/or prevention of neurodegenerative disorders including Huntington's chorea, Alzheimer's disease, other types of dementia, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia and hypoxia, spinal or head trauma and epilepsy. A selected compound from a series of thiophene-sulfonamide derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

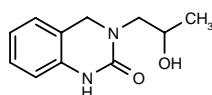
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RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

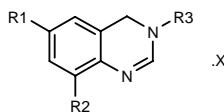
277563

(±)-3-(2-Hydroxypropyl)-1,2,3,4-tetrahydroquinazolin-2-one

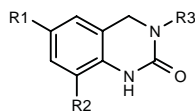


C11 H14 N2 O2; Mol wt: 206.2436

ACTION – Expectorant proven to be more potent than ambroxol in increasing tracheal fluid secretion in mice following oral administration. Other compounds from this series of quinazoline derivatives include the following:



Compound	R1=R2	R3	Isomer	X	Formula
277564	H	CH2CH(OH)Me	racemic	oxalate	C ₁₁ H ₁₄ N ₂ O .C ₂ H ₂ O ₄
277565	Br	CH2CH(OH)Me	racemic	HCl	C ₁₁ H ₁₂ Br ₂ N ₂ O .HCl
277568	Br	trans-2-OH-cyclohexyl	racemic	oxalate	C ₁₄ H ₁₆ Br ₂ N ₂ O .C ₂ H ₂ O ₄



Compound	R1=R2	R3	Isomer	Formula
277567	Br	CH2CH(OH)Me	racemic	C ₁₁ H ₁₂ Br ₂ N ₂ O ₂
277569	H	trans-2-OH-cyclohexyl	racemic	C ₁₄ H ₁₈ N ₂ O ₂

SOURCE – Sawai.

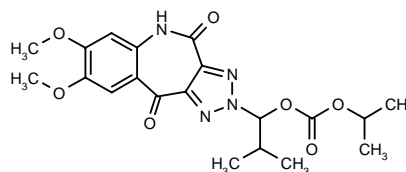
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ASTHMA THERAPY

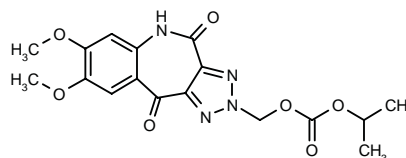
276224

2-[1-(Isopropoxycarbonyloxy)-2-methylpropyl]-7,8-dimethoxy-2,4,5,10-tetrahydro[1,2,3]triazolo[4,5-c][1]benzazepine-4,10-dione



C20 H24 N4 O7; Mol wt: 432.4306

ACTION – Antiallergic agent reported to possess excellent oral bioavailability and safety, no mortality being observed following a single dose of 2 g/kg p.o. to mice. Another compound from this series of tricyclic triazolo-benzazepine derivatives is:



276225: C17 H18 N4 O7

SOURCE – Meiji Seika.

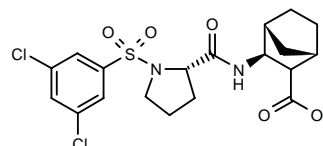
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277197

3*exo*-3-[1-(3,5-Dichlorophenylsulfonyl)pyrrolidin-2(S)-ylcarboxamido]bicyclo[2.2.1]heptane-2-carboxylic acid

N-(2-Carboxybicyclo[2.2.1]heptan-3*exo*-yl)-1-(3,5-dichlorophenylsulfonyl)-L-prolinamide



C19 H22 Cl2 N2 O5 S; Mol wt: 461.3638

ACTION – Kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor ($IC_{50} = 10.4 \mu M$ for inhibition of rat liver mitochondrial enzyme) expected to be useful in the treatment and/or prevention of neurodegenerative disorders including Huntington's chorea, Alzheimer's disease, other types of dementia, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia and hypoxia, spinal or head trauma and epilepsy. A selected compound from a series of thiophene-sulfonamide derivatives.

SOURCE – Pharmacia & Upjohn.

REFERENCES

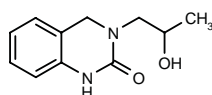
1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *Thiophene-sulfonamide cpds.* WO 9928316.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

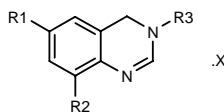
277563

(±)-3-(2-Hydroxypropyl)-1,2,3,4-tetrahydroquinazolin-2-one

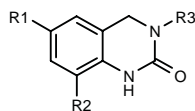


C11 H14 N2 O2; Mol wt: 206.2436

ACTION – Expectorant proven to be more potent than ambroxol in increasing tracheal fluid secretion in mice following oral administration. Other compounds from this series of quinazoline derivatives include the following:



Compound	R1=R2	R3	Isomer	X	Formula
277564	H	CH2CH(OH)Me	racemic	oxalate	C ₁₁ H ₁₄ N ₂ O .C ₂ H ₂ O ₄
277565	Br	CH2CH(OH)Me	racemic	HCl	C ₁₁ H ₁₂ Br ₂ N ₂ O .HCl
277568	Br	trans-2-OH-cyclohexyl	racemic	oxalate	C ₁₄ H ₁₆ Br ₂ N ₂ O .C ₂ H ₂ O ₄



Compound	R1=R2	R3	Isomer	Formula
277567	Br	CH2CH(OH)Me	racemic	C ₁₁ H ₁₂ Br ₂ N ₂ O ₂
277569	H	trans-2-OH-cyclohexyl	racemic	C ₁₄ H ₁₈ N ₂ O ₂

SOURCE – Sawai.

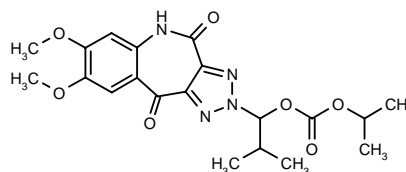
REFERENCES

1. Koya, H. et al. (Sawai Pharmaceutical Co., Ltd.) *Novel quinazoline derivs. and their medicinal use.* JP 99124369.

ASTHMA THERAPY

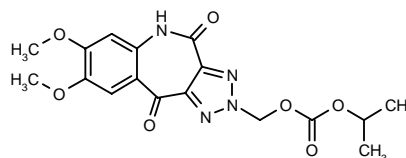
276224

2-[1-(Isopropoxycarbonyloxy)-2-methylpropyl]-7,8-dimethoxy-2,4,5,10-tetrahydro[1,2,3]triazolo[4,5-c][1]benzazepine-4,10-dione



C20 H24 N4 O7; Mol wt: 432.4306

ACTION – Antiallergic agent reported to possess excellent oral bioavailability and safety, no mortality being observed following a single dose of 2 g/kg p.o. to mice. Another compound from this series of tricyclic triazolo-benzazepine derivatives is:



276225: C17 H18 N4 O7

SOURCE – Meiji Seika.

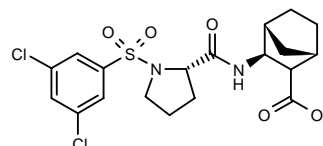
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277197

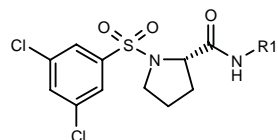
3*exo*-3-[1-(3,5-Dichlorophenylsulfonyl)pyrrolidin-2(S)-ylcarboxamido]bicyclo[2.2.1]heptane-2-carboxylic acid

N-(2-Carboxybicyclo[2.2.1]heptan-3*exo*-yl)-1-(3,5-dichlorophenylsulfonyl)-L-prolinamide

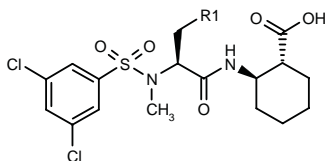


C19 H22 Cl2 N2 O5 S; Mol wt: 461.3638

ACTION – VLA-4 (very late antigen-4, CD49d/CD28, $\alpha_4\beta_1$) and/or $\alpha_4\beta_7$ (LPAM-1, $\alpha_4\beta_p$) integrin antagonist useful for inhibiting or preventing cell adhesion and related pathologies. Title compound blocks the binding of VLA-4 and/or $\alpha_4\beta_7$ to their ligands including VCAM-1 and fibronectin. Potentially useful in the treatment of asthma, allergic rhinitis, multiple sclerosis, inflammation and inflammatory bowel disease. Other specifically claimed cyclic amino acid derivatives include the following:



Compound	R1	Formula
277198	cis-2-CO2H-cyclohexyl	C ₁₈ H ₂₂ Cl ₂ N ₂ O ₅ S
277201	2-CO2H-1-cyclopentenyl	C ₁₇ H ₁₈ Cl ₂ N ₂ O ₅ S
277202	2-CO2H-5-bicyclo-[2.2.1]hept-5-en-3-endo-yl	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₅ S
277205	2-CO2H-bicyclo[2.2.2]oct-3-endo-yl	C ₂₀ H ₂₄ Cl ₂ N ₂ O ₅ S



Compound	R1	Formula
277203	Me	C ₁₉ H ₂₆ Cl ₂ N ₂ O ₅ S
277204	Ph	C ₂₃ H ₂₆ Cl ₂ N ₂ O ₅ S

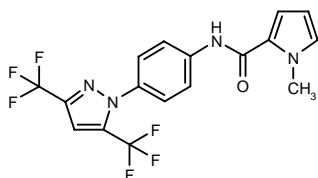
SOURCE – Merck & Co.

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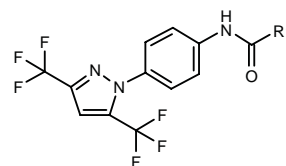
277223

N-[4-[3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-1-methyl-1*H*-pyrrole-2-carboxamide

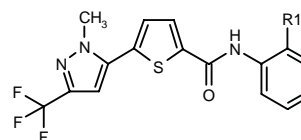


C₁₇ H₁₂ F₆ N₄ O; Mol wt: 402.2968

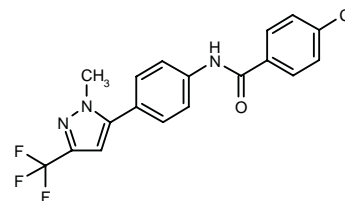
ACTION – Selective calcium (Ca²⁺) release-activated calcium (Ca²⁺) channel (CRACC) inhibitor (IC₅₀ = 0.050-0.51 μ M in Jurkat cells) showing 16- to over 200-fold selectivity relative to voltage-dependent Ca²⁺ channels (VOCC). It also inhibited IL-2 production in Jurkat cells with IC₅₀ values of 1 μ M or less. Potentially useful in the treatment of bronchial asthma, psoriasis, atopic dermatitis, inflammatory bowel disease, peptic ulcer, nephritis, hepatitis, pancreatitis, rheumatoid arthritis, osteoarthritis and transplant rejection. Other exemplified pyrazole derivatives include the following:



Compound	R1	Formula
277224	4-Me-5-thiazolyl	C ₁₆ H ₁₀ F ₆ N ₄ OS
277227	3-Me-2-thienyl	C ₁₇ H ₁₁ F ₆ N ₃ OS
277229	3-Pyr	C ₁₇ H ₁₀ F ₆ N ₄ O



Compound	R1	Formula
277226	Cl	C ₁₆ H ₁₁ ClF ₃ N ₃ OS
277230	Me	C ₁₇ H ₁₄ F ₃ N ₃ OS
277232	H	C ₁₆ H ₁₂ F ₃ N ₃ OS



277233: C₁₈ H₁₃ Cl F₃ N₃ O

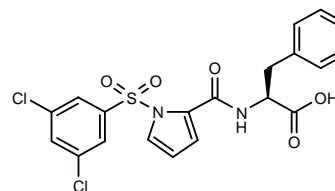
SOURCE – Yamanouchi.

REFERENCES

- Kubota, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Pyrazole derivs*. WO 9919303.

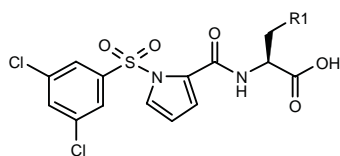
277485

N-[1-(3,5-Dichlorophenylsulfonyl)-1*H*-pyrrol-2-yl]carboxyl-L-phenylalanine



C₂₀ H₁₆ Cl₂ N₂ O₅ S; Mol wt: 467.3274

ACTION – Cell adhesion inhibitor that inhibits the binding of VLA-4 (very late antigen-4, CD49d/CD29, $\alpha_4\beta_1$) and/or $\alpha_4\beta_7$ (LPAM-1, $\alpha_4\beta_p$) integrins to their ligands including VCAM-1 and fibronectin (IC₅₀ < 10 nM against VCAM-Ig binding to VLA-4). Potentially useful in the treatment of pathological conditions characterized by cell adhesion and activation such as asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, inflammation and inflammatory bowel disease. Other exemplified substituted pyrrole derivatives are:



Compound	R1	Formula
277486	CH2Ph	C ₂₁ H ₁₈ Cl ₂ N ₂ O ₅ S
277490	Pr	C ₁₇ H ₁₆ Cl ₂ N ₂ O ₅ S
277491	4-t-BuO-Ph	C ₂₄ H ₂₄ Cl ₂ N ₂ O ₆ S
277492	4-(PhCH2O)-Ph	C ₂₇ H ₂₂ Cl ₂ N ₂ O ₆ S
277493	4-(2-MeO-Ph)-Ph	C ₂₇ H ₂₂ Cl ₂ N ₂ O ₆ S
277494	4-(3-MeO-Ph)-Ph	C ₂₇ H ₂₂ Cl ₂ N ₂ O ₆ S
277495	4-(2-CN-Ph)-Ph	C ₂₇ H ₁₉ Cl ₂ N ₃ O ₅ S

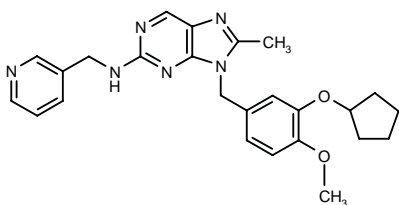
SOURCE – Merck & Co.

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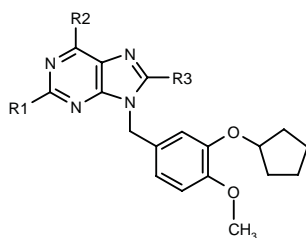
277726

N-[9-(3-Cyclopentyloxy-4-methoxybenzyl)-8-methyl-9*H*-purin-2-yl]-*N*-(pyridin-3-ylmethyl)amine



C25 H28 N6 O2; Mol wt: 444.5362

ACTION – Antiasthmatic agent, a phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 1.0 nM using PDE4 from human U937 cells). Other exemplified purine derivatives include the following:



Compound	R1	R2	R3	Formula
277727	2-furyl-CH2NH	H	H	C ₂₃ H ₂₅ N ₅ O ₃
277739	2-Pyr-CH2NH	H	Me	C ₂₅ H ₂₈ N ₆ O ₂
277740	4-Pyr-(CH2)3O	H	Me	C ₂₇ H ₃₁ N ₅ O ₃
277741	4-Pyr-(CH2)3O	NH2	H	C ₂₆ H ₃₀ N ₆ O ₃
277742	6-(CF3CH2O)-3-Pyr-CH2O	H	Me	C ₂₇ H ₂₆ F ₃ N ₅ O ₄
277743	2-thienyl-CH2NH	Me	H	C ₂₄ H ₂₇ N ₅ O ₂ S
277744	4-Pyr-CH2NH	Me	Me	C ₂₆ H ₃₀ N ₆ O ₂
277745	1-oxido-4-Pyr-CH2O	Me	Me	C ₂₆ H ₂₉ N ₅ O ₄
277746	3-Pyr-CH2NH	N(Me)2	H	C ₂₆ H ₃₁ N ₇ O ₂
277747	1-oxido-4-Pyr-(CH2)3O	NHEt	H	C ₃₀ H ₃₈ N ₆ O ₄

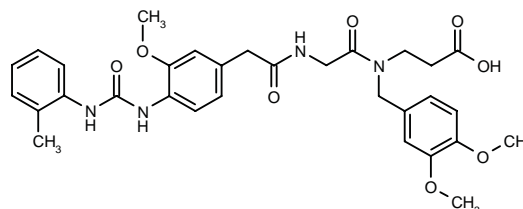
SOURCE – Mitsubishi Chemical.

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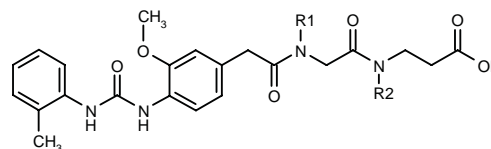
278613

3-[*N*-(3,4-Dimethoxybenzyl)-*N*-[2-[2-[3-methoxy-4-(3-(2-methylphenyl)ureido]phenyl]acetamido]acetyl]amino]-propionic acid



C31 H36 N4 O8; Mol wt: 592.6454

ACTION – Agent for the treatment of inflammation, cancer, autoimmune diseases, atherosclerosis and, particularly, asthma that acts by inhibiting the interaction between vascular cell adhesion molecule-1 (VCAM-1) and fibronectin with the $\alpha_4\beta_1$ integrin receptor (also known as very late antigen-4 or VLA-4). Other specifically claimed compounds from this series of substituted β -alanines include the following:



Compound	R1	R2	Formula
278614	Me	2-oxo-1-pyrrolidinyl-(CH2)3	C ₃₀ H ₃₉ N ₅ O ₇
278615	Me	3,4-(MeO)2-PhCH2	C ₃₂ H ₃₈ N ₄ O ₈
278616	H	2-oxo-1-pyrrolidinyl-(CH2)3	C ₂₉ H ₃₇ N ₅ O ₇
278617	H	2,3-(MeO)2-PhCH2	C ₃₁ H ₃₆ N ₄ O ₈
278618	Me	(CH2)3CO2H	C ₂₇ H ₃₄ N ₄ O ₈
278619	H	3-EtO-4-MeO-PhCH2	C ₃₂ H ₃₈ N ₄ O ₈
278620	H	3,4-(EtO)2-PhCH2	C ₃₃ H ₄₀ N ₄ O ₈

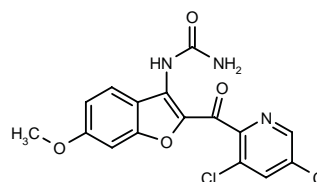
SOURCE – Rhône-Poulenc Rorer.

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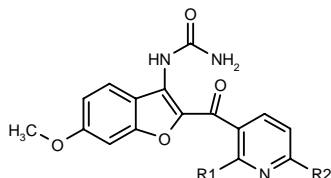
278788

N-[2-(3,5-Dichloropyridin-2-ylcarbonyl)-6-methoxy-1-benzofuran-3-yl]urea



C16 H11 Cl2 N3 O4; Mol wt: 380.1859

ACTION – Antiinflammatory agent that acts by inhibiting oxygen radical formation and TNF- α production. Compound was found to inhibit fMLP-stimulated production of superoxide by human polymorphonuclear leukocytes and to inhibit TNF- α release in human monocytes stimulated with bacterial lipopolysaccharide, complement-opsonized zymosan and IL-1 β ; these effects appear to be mediated by elevated cellular cAMP levels, probably due to inhibition of type 4 phosphodiesterase (PDE4). Other specifically claimed compounds from this series of 3-ureidobenzofuran derivatives include the following:



Compound	R1	R2	Formula
278789	Me	Me	C ₁₈ H ₁₇ N ₃ O ₄
278790	H	H	C ₁₆ H ₁₃ N ₃ O ₄

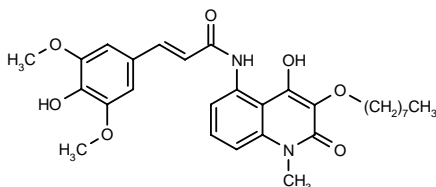
SOURCE – Bayer.

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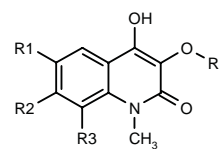
278827

3-(4-Hydroxy-3,5-dimethoxyphenyl)-N-(4-hydroxy-1-methyl-3-octyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2(E)-propenamide



C₂₉ H₃₆ N₂ O₇; Mol wt: 524.6104

ACTION – Antiallergic agent, as demonstrated by 55% inhibition of the passive cutaneous anaphylaxis (PCA) reaction in rats at 100 mg/kg p.o. LD₅₀ > 1000 mg/kg p.o. in mice. Potentially useful for the treatment of asthma, atopic dermatitis, allergic dermatitis, urticaria, eczema, allergic conjunctivitis, allergic rhinitis, food allergy and the like. Within this series of quinolin-2(1H)-one derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
278828	NHC10H21	H	H	Me	C ₂₁ H ₃₂ N ₂ O ₃
278829	OC10H21	H	H	Me	C ₂₁ H ₃₁ NO ₄
278830	H	NHAc	H	C8H17	C ₂₀ H ₂₈ N ₂ O ₄
278831	(E)-3,5-(OMe)2-4-OH-PhCH=CHCONH	H	H	C8H17	C ₂₉ H ₃₈ N ₂ O ₇
278832	H	H	OC6H13	C6H13	C ₂₂ H ₃₃ NO ₄
278833	H	H	NHMe	C8H17	C ₁₉ H ₂₈ N ₂ O ₃

SOURCE – Dainippon Ink & Chemicals.

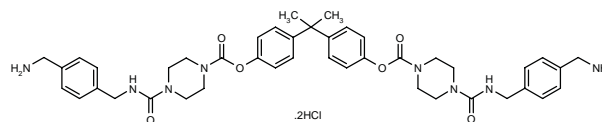
REFERENCES

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279929

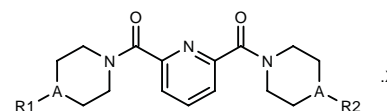
2,2-Bis[4-[4-[N-[4-(aminomethyl)benzyl]carbamoyl]piperazin-1-ylcarbonyloxy]phenyl]propane dihydrochloride

4,4'-Isopropylidenebis(1,4-phenylenedioxy)bis(carbonyl)-bis[N-[4-(aminomethyl)benzyl]piperazine-1-carboxamide] dihydrochloride

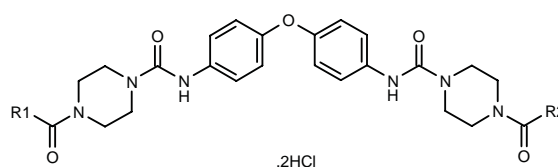


C₄₃ H₅₂ N₈ O₆ · 2HCl; Mol wt: 849.8556

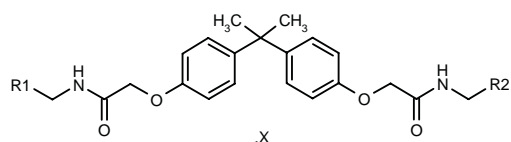
ACTION – Human tryptase inhibitor giving a K_i value of 0.028 μ M against human enzyme, expected to be useful in the treatment of respiratory disorders such as bronchitis, asthma, etc. Other exemplified compounds include the following:



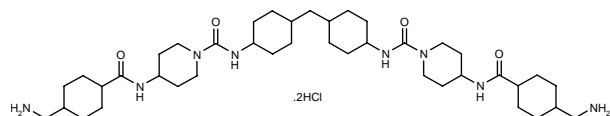
Compound	R1=R2	A	X	Formula
279930	3-(NH ₂ CH ₂)-PhCO	N	3HCl	C ₃₁ H ₃₅ N ₇ O ₄ ·3HCl
279931	3-(NH ₂ CH ₂)-PhCONH	CH		C ₃₃ H ₃₉ N ₇ O ₄
279932	trans-4-(NH ₂ CH ₂)-cyclohexyl-CONH	CH		C ₃₃ H ₄₁ N ₇ O ₄



Compound	R1=R2	Formula
279933	4-(NH ₂ CH ₂)-cyclohexyl	C ₃₈ H ₅₄ N ₈ O ₅ ·2HCl
279934	3-(NH ₂ CH ₂)-Ph	C ₃₈ H ₄₂ N ₈ O ₅ ·2HCl



Compound	R1=R2	X	Formula
279936	4-[NH ₂ C(=NH)NH]-Ph	.2CH ₃ CO ₂ H	C ₃₆ H ₄₀ N ₈ O ₄ .2C ₂ H ₄ O ₂
279937	CONH(CH ₂) ₄ NH ₂	.2HCl	C ₃₁ H ₄₆ N ₆ O ₆ .2HCl



279935: C₄₁ H₇₂ N₈ O₄ . 2HCl

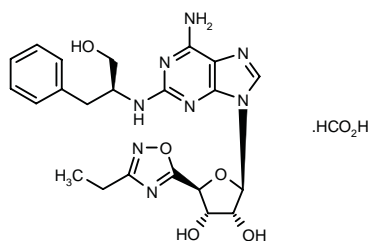
SOURCES – Byk Gulden; Max-Planck-Gesellschaft, München (DE).

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1. Bode, W. et al. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.; Byk Gulden Lomberg Chemische Fabrik GmbH) *Tryptase inhibitors*. DE 19851299, WO 9940083.

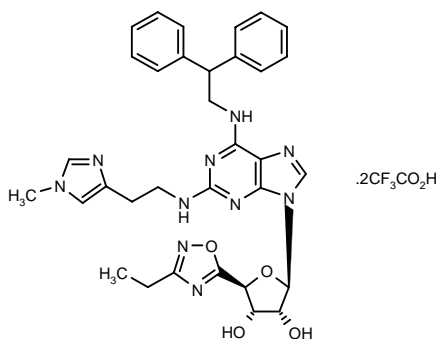
279950

(2*R*,3*R*,4*S*,5*S*)-2-[6-Amino-2-[1(*S*)-benzyl-2-hydroxy-ethylamino]-9*H*-purin-9-yl]-5-(3-ethyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate



C₂₂ H₂₆ N₈ O₅ . C H₂ O₂; Mol wt: 528.5232

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as an adenosine A_{2A} receptor agonist. It may have an improved profile over known adenosine A_{2A}-selective agonists in that it lacks agonist activity at the human adenosine A₃ receptor and may even exert antagonist activity at this receptor. It is therefore of potential therapeutic benefit in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease. Another specifically claimed 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivative is:



279951: C₃₃ H₃₆ N₁₀ O₄ . 2 C₂ H F₃ O₂

SOURCE – Glaxo Wellcome.

REFERENCES

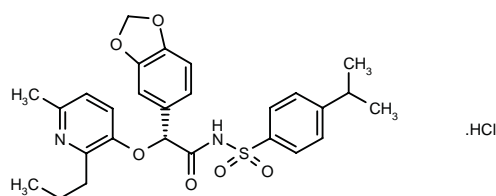
1. Chan, C. et al. (Glaxo Group Ltd.) *2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs*. WO 9941267.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

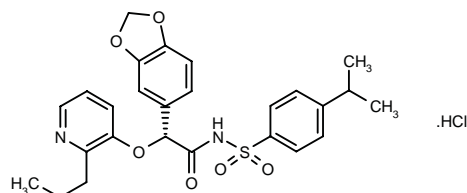
260272¹⁻⁴

(-)-2(*R*)-(1,3-Benzodioxol-5-yl)-*N*-(4-isopropylphenyl)sulfonyl)-2-(6-methyl-2-propylpyridin-3-yloxy)acetamide hydrochloride

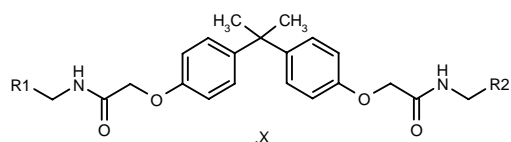


C₂₇ H₃₀ N₂ O₆ S . HCl; Mol wt: 547.0689

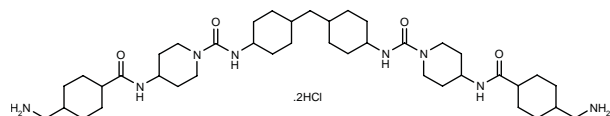
ACTION – Potent, nonpeptide endothelin ET_A receptor antagonist (K_i = 0.11 nM) with at least 200-fold selectivity over ET_B receptors (K_i = 25 nM). Compound showed functional antagonist activity against ET-1-induced contractions in isolated endothelium-denuded rabbit femoral arteries (K_b = 0.46 nM) and ET-3-induced relaxation of phenylephrine-precontracted endothelium-intact rat mesenteric arteries (K_b = 26.0 nM). Compound given orally inhibited the pressor response to ET-1 (ED₅₀ = 2.2 mg/kg) in normotensive rats, with no significant effect on basal blood pressure. In DOCA-salt hypertensive rats, spontaneously hypertensive rats and stroke-prone spontaneously hypertensive rats, compound (10-100 mg/kg p.o.) dose-dependently reduced systolic blood pressure with a slow onset (6 h after administration) and long duration of action (> 24 h). Potentially useful for the treatment of ET-related diseases such as pulmonary hypertension, congestive heart failure and cerebral vasospasm after subarachnoid hemorrhage. Another related compound is:



260273^{1,2,4}: C₂₆ H₂₈ N₂ O₆ S . HCl



Compound	R1=R2	X	Formula
279936	4-[NH ₂ C(=NH)NH]-Ph	.2CH ₃ CO ₂ H	C ₃₆ H ₄₀ N ₈ O ₄ .2C ₂ H ₄ O ₂
279937	CONH(CH ₂) ₄ NH ₂	.2HCl	C ₃₁ H ₄₆ N ₆ O ₆ .2HCl



279935: C₄₁ H₇₂ N₈ O₄ . 2HCl

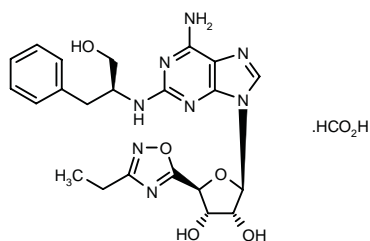
SOURCES – Byk Gulden; Max-Planck-Gesellschaft, München (DE).

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1. Bode, W. et al. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.; Byk Gulden Lomberg Chemische Fabrik GmbH) *Tryptase inhibitors*. DE 19851299, WO 9940083.

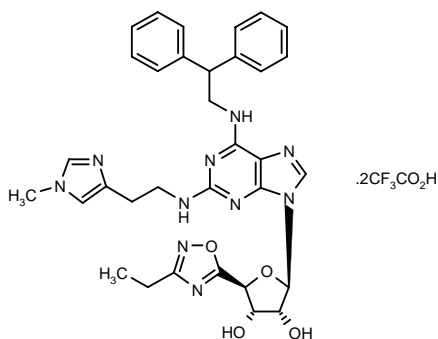
279950

(2*R*,3*R*,4*S*,5*S*)-2-[6-Amino-2-[1(*S*)-benzyl-2-hydroxy-ethylamino]-9*H*-purin-9-yl]-5-(3-ethyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate



C₂₂ H₂₆ N₈ O₅ . C H₂ O₂; Mol wt: 528.5232

ACTION – Antiinflammatory agent that inhibits leukocyte recruitment and activation and acts as an adenosine A_{2A} receptor agonist. It may have an improved profile over known adenosine A_{2A}-selective agonists in that it lacks agonist activity at the human adenosine A₃ receptor and may even exert antagonist activity at this receptor. It is therefore of potential therapeutic benefit in inflammatory diseases in which leukocytes are implicated, particularly asthma and chronic obstructive pulmonary disease. Another specifically claimed 2-(purin-9-yl)tetrahydrofuran-3,4-diol derivative is:



279951: C₃₃ H₃₆ N₁₀ O₄ . 2 C₂ H F₃ O₂

SOURCE – Glaxo Wellcome.

REFERENCES

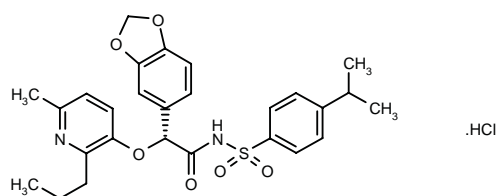
1. Chan, C. et al. (Glaxo Group Ltd.) *2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivs*. WO 9941267.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

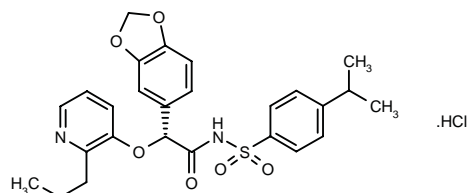
260272¹⁻⁴

(-)-2(*R*)-(1,3-Benzodioxol-5-yl)-*N*-(4-isopropylphenyl)sulfonyl)-2-(6-methyl-2-propylpyridin-3-yloxy)acetamide hydrochloride



C₂₇ H₃₀ N₂ O₆ S . HCl; Mol wt: 547.0689

ACTION – Potent, nonpeptide endothelin ET_A receptor antagonist (K_i = 0.11 nM) with at least 200-fold selectivity over ET_B receptors (K_i = 25 nM). Compound showed functional antagonist activity against ET-1-induced contractions in isolated endothelium-denuded rabbit femoral arteries (K_b = 0.46 nM) and ET-3-induced relaxation of phenylephrine-precontracted endothelium-intact rat mesenteric arteries (K_b = 26.0 nM). Compound given orally inhibited the pressor response to ET-1 (ED₅₀ = 2.2 mg/kg) in normotensive rats, with no significant effect on basal blood pressure. In DOCA-salt hypertensive rats, spontaneously hypertensive rats and stroke-prone spontaneously hypertensive rats, compound (10-100 mg/kg p.o.) dose-dependently reduced systolic blood pressure with a slow onset (6 h after administration) and long duration of action (> 24 h). Potentially useful for the treatment of ET-related diseases such as pulmonary hypertension, congestive heart failure and cerebral vasospasm after subarachnoid hemorrhage. Another related compound is:



260273^{1,2,4}: C₂₆ H₂₈ N₂ O₆ S . HCl

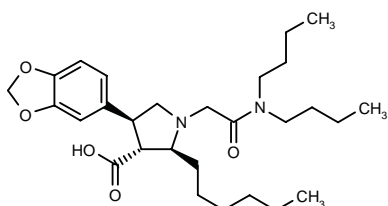
SOURCE – Shionogi.

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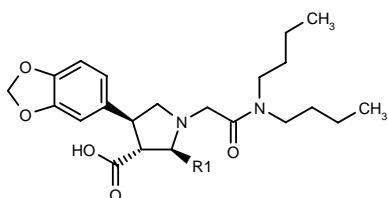
2780872-4

(2*S*^{*},3*R*^{*},4*S*^{*})-4-(1,3-Benzodioxol-5-yl)-1-(*N,N*-dibutyl-carbamoylmethyl)-2-hexylpyrrolidine-3-carboxylic acid



C28 H44 N2 O5; Mol wt: 488.6646

ACTION – Endothelin receptor antagonist with high selectivity for ET_A over ET_B receptors (IC₅₀ = 0.0056 and 18.7 μM, respectively), potentially useful for the treatment of cardiovascular diseases including hypertension, congestive heart failure, vasospasm, restenosis following angioplasty, subarachnoid hemorrhage, ischemia, pulmonary hypertension and renal failure. Within this series of pyrrolidines, the following are also included:



Compound	R1	Formula
278086 ¹⁻⁵	C5H11	C ₂₇ H ₄₂ N ₂ O ₅
278088 ²⁻⁴	4-Me-cyclohexyl	C ₂₉ H ₄₄ N ₂ O ₅

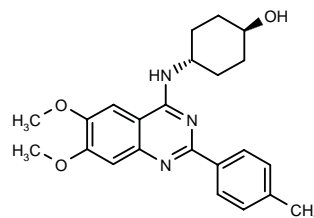
SOURCE – Abbott.

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- Liu, G. et al. *Pyrrolidine-3-carboxylic acids as endothelin antagonists. 3. Discovery of a potent, 2-nonaryl, highly selective ETA antagonist (A-216546)*. J Med Chem 1998, 41(17): 3261.

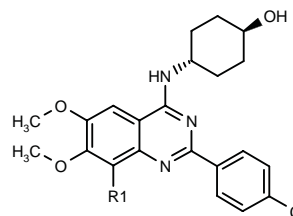
278280

trans-4-[6,7-Dimethoxy-2-(4-methylphenyl)quinazolin-4-ylamino]cyclohexanol



C23 H27 N3 O3; Mol wt: 393.4843

ACTION – Agent for the treatment of disorders involving low cGMP levels such as hypertension, angina pectoris, congestive heart failure, thrombosis, atherosclerosis, restenosis, stroke, erectile dysfunction, bronchial asthma, renal failure and diabetes. *In vitro*, compound was shown to produce a 16-fold increase in cGMP levels at 50 μM using an enzyme immunoassay. Other compounds from this series of substituted 2-aryl-4-aminoquinazolines include the following:



Compound	R1	Formula
278281	H	C ₂₂ H ₂₄ ClN ₃ O ₃
278282	OMe	C ₂₃ H ₂₆ ClN ₃ O ₄

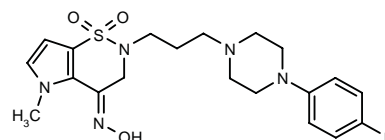
SOURCE – Hoechst Marion Roussel.

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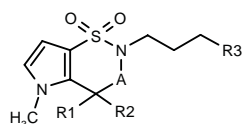
278625

2-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-(hydroxyimino)-5-methyl-2,3,4,5-tetrahydropyrrolo[2,3-e]-1,2-thiazine 1,1-dioxide



C20 H26 F N5 O3 S; Mol wt: 435.5214

ACTION – Antihypertensive and antiischemic agent with 5-HT₂ receptor- and α_1 -adrenoceptor-antagonist activity; 5-HT₂-antagonist effects were evaluated by measuring inhibition of 5-HT-induced contractions of guinea pig superior mesenteric artery (69.8 and 16.6% of control [taken as 100%] at concentrations of 0.1 and 1 μ M, respectively) and α_1 -blocking effects were determined by measuring inhibition of norepinephrine-induced contractions of guinea pig thoracic aorta (65.3 and 24.1% of control [taken as 100%] at concentrations of 0.01 and 0.1 μ M, respectively). Other compounds within this series of pyrrolothiazine and pyrrolothiazepine derivatives include the following:



Compound	R1	R2	R3	A	Formula
278626		-O-	4-(4-F-PhCO)-1-Pip	-(CH2)2-	C ₂₃ H ₂₈ FN ₃ O ₄ S
278627	OH	H	4-(4-F-Ph)-1-Piz	-(CH2)2-	C ₂₁ H ₂₉ FN ₄ O ₃ S
278628	-N(OH)-		4-(4-F-PhCO)-1-Pip	-CH2-	C ₂₂ H ₂₇ FN ₄ O ₄ S
278629	-N(OH)-		4-(4-F-Ph)-1-Piz	-(CH2)2-	C ₂₁ H ₂₈ FN ₅ O ₃ S

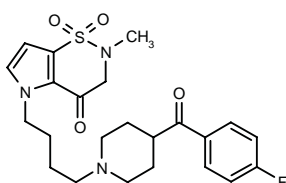
SOURCE – Suntory.

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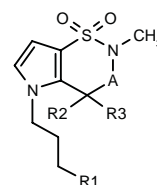
278630

5-[4-[4-(4-Fluorobenzoyl)piperidin-1-yl]butyl]-2-methyl-2,3,4,5-tetrahydropyrrolo[2,3-e]-1,2-thiazin-4-one 1,1-dioxide



C₂₃ H₂₈ F N₃ O₄ S; Mol wt: 461.5552

ACTION – Antihypertensive and antiischemic agent with 5-HT₂ receptor- and α_1 -adrenoceptor-antagonist activity; 5-HT₂-antagonist effects were evaluated by measuring inhibition of 5-HT-induced contractions of guinea pig superior mesenteric artery (80.4 and 41.1% of control [taken as 100%] at concentrations of 0.1 and 1 μ M, respectively) and α_1 -blocking effects were determined by measuring inhibition of norepinephrine-induced contractions of guinea pig thoracic aorta (66.6 and 43.2% of control [taken as 100%] at concentrations of 0.01 and 0.1 μ M, respectively). Other compounds within this series of pyrrolothiazine and pyrrolothiazepine derivatives include the following:



Compound	R1	R2	R3	A	Formula
278631	4-(4-F-Ph)-1-Piz	-O-	-(CH2)2-		C ₂₁ H ₂₇ FN ₄ O ₃ S
278632	4-(4-F-PhCO)-1-Pip-CH2	-N(OH)-	-CH2-		C ₂₃ H ₂₉ FN ₄ O ₄ S
278633	4-(4-F-PhCO)-1-Pip-CH2	-N(OH)-	-(CH2)2-		C ₂₄ H ₃₁ FN ₄ O ₄ S

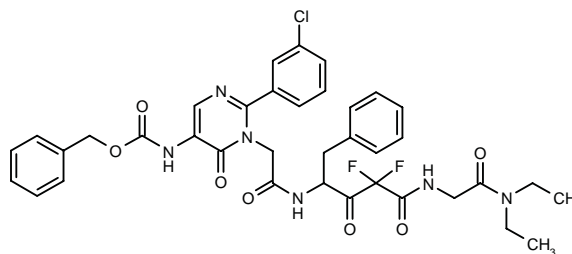
SOURCE – Suntory.

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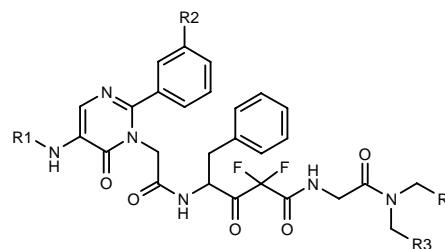
279250

4-[2-[5-(Benzyloxycarbonylamino)-2-(3-chlorophenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]acetamido]-N-[2-(diethylamino)-2-oxoethyl]-2,2-difluoro-3-oxo-5-phenylpentanamide



C₃₇ H₃₇ Cl F₂ N₆ O₇; Mol wt: 751.1833

ACTION – Agent for the treatment of angiotensin II-mediated disorders, a potent and selective inhibitor of human cardiac chymase (K_i = 0.149 nM) with no activity on human leukocyte elastase. Other compounds from this series of heterocyclic amide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279251	H	Me	-(CH2)4-		C ₃₂ H ₃₆ F ₂ N ₆ O ₅
279252	CO ₂ CH ₂ Ph	Me	-(CH2)2-		C ₃₈ H ₃₈ F ₂ N ₆ O ₇
279253	CO ₂ CH ₂ Ph	F	Me	Me	C ₃₇ H ₃₇ F ₃ N ₆ O ₇
279254	H	Cl	Me	Me	C ₂₉ H ₃₁ ClF ₂ N ₆ O ₅
279255	Ac	Me	Me	Me	C ₃₂ H ₃₆ F ₂ N ₆ O ₆

SOURCE – Yoshitomi.

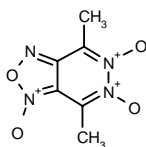
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FPTO

277196

4,7-Dimethyl-1,2,5-oxadiazolo[3,4-*d*]pyridazine 1,5,6-trioxide



C₆ H₆ N₄ O₄; Mol wt: 198.1374

ACTION – Vasodilating agent, a nitric oxide (NO) donor proven to relax rat thoracic aortic rings, exhibiting a biphasic dose–response curve ($pIC_{50} = 9.03$ and 5.85); its vasorelaxant effect appears to involve the soluble guanylate cyclase (sGC)-NO pathway. *In vivo*, compound produced a dose-dependent (40 – 120 $\mu\text{g/kg}$ i.v.) and transient decrease in blood pressure in conscious normotensive rats, with no development of tolerance upon repeated injection. Glycyrrhizic acid, glycyrrhizic acid ammonium salt and β -cyclodextrin complexes of FPTO show enhanced water solubility and improved stability compared to the free compound and were approximately equipotent in inducing relaxation of rat thoracic aorta rings. Particularly, the glycyrrhizic acid complex exerted comparable blood pressure-lowering effects to the free compound, without the delayed increase in blood pressure and heart rate observed with FPTO. Potentially useful for the treatment of cardiovascular disorders such as hypertension.

SOURCES – Institute of Organic Chemistry, Moscow (RU); M.V. Lomonosov Moscow State University, Moscow (RU).

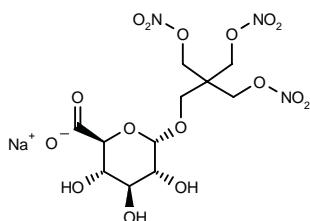
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

276132

1-*O*-[3-Nitrooxy-2,2-bis(nitrooxymethyl)propyl]- α -D-glucopyranuronic acid sodium salt



C₁₁ H₁₆ N₃ Na O₁₆; Mol wt: 469.2424

ACTION – A representative compound from a series of nitric esters of pentaerythritol, potentially useful for the treatment of cardiovascular disorders, oxidative stress, as well as for use as a vasodilating agent and platelet aggregation inhibitor.

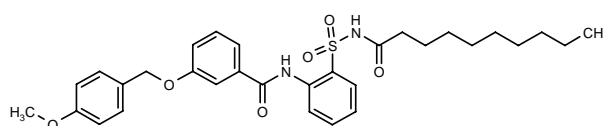
SOURCES – Isis Pharmaceuticals; Schwarz.

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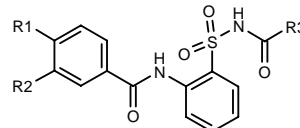
279157

N-[2-(Decanamidosulfonyl)phenyl]-3-(4-methoxybenzyl-oxy)benzamide



C₃₁ H₃₈ N₂ O₆ S; Mol wt: 566.7152

ACTION – An inhibitor of acetyl-CoA carboxylase (ACC; 81.6% inhibition at 5.6 μM using enzyme from rat liver), proven to inhibit fatty acid biosynthesis in HepG2 cells (92.0% inhibition at 30 μM). Potentially useful for the treatment of myocardial and cerebral infarction and diabetes. Other compounds from this series of acylsulfonamide derivatives include the following:



Compound	R1	R2	R3	Formula
279158	NO ₂	OCH ₂ Ph	C ₉ H ₁₉	C ₃₀ H ₃₅ N ₃ O ₇ S
279159	H	4-Cl-Ph-CH ₂ O	C ₉ H ₁₉	C ₃₀ H ₃₅ ClN ₂ O ₅ S
279160	H	4-NO ₂ -Ph-CH ₂ O	C ₉ H ₁₉	C ₃₀ H ₃₅ N ₃ O ₇ S
279161	H	4-CF ₃ -Ph-CH ₂ O	C ₅ H ₁₁	C ₂₇ H ₂₇ F ₃ N ₂ O ₅ S
279162	Ph-ethynylene	H	C ₅ H ₁₁	C ₂₇ H ₂₆ N ₂ O ₄ S
279163	Ph-ethynylene	H	(E,E)-CH=CH-CH=CHMe	C ₂₇ H ₂₂ N ₂ O ₄ S

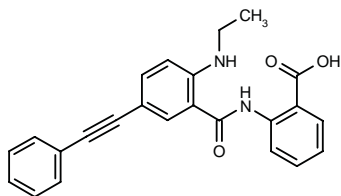
SOURCE – Fujirebio.

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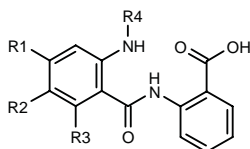
279164

2-[2-(Ethylamino)-5-(2-phenylethynyl)benzamido]benzoic acid



C₂₄ H₂₀ N₂ O₃; Mol wt: 384.4330

ACTION – An inhibitor of acetyl-CoA carboxylase (ACC; 86.5% inhibition at 5.6 μM using enzyme from rat liver), proven to inhibit fatty acid biosynthesis in HepG2 cells (98.3% inhibition at 30 μM). Potentially useful for the treatment of myocardial and cerebral infarction and diabetes. Other compounds from this series of aromatic amide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279165	OCH ₂ Ph	H	H	Ph	C ₂₇ H ₂₂ N ₂ O ₄
279166	H	H	NHC ₆ H ₁₃	C ₆ H ₁₃	C ₂₆ H ₃₇ N ₃ O ₃
279167	H	Ph-ethynylene	H	Me	C ₂₃ H ₁₈ N ₂ O ₃
279168	H	Ph-ethynylene	H	Pr	C ₂₅ H ₂₂ N ₂ O ₃

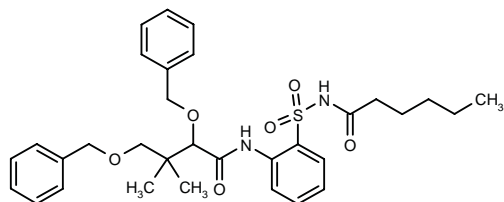
SOURCE – Fujirebio.

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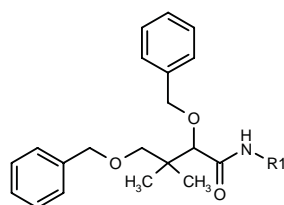
279243

2,4-Bis(benzyloxy)-N-[2-(hexanamidossulfonyl)phenyl]-3,3-dimethylbutyramide



C₃₂ H₄₀ N₂ O₆ S; Mol wt: 580.7420

ACTION – An inhibitor of acetyl-CoA carboxylase (ACC; 98.6% inhibition at 30 μM using enzyme from rat liver), potentially useful for the treatment of myocardial and cerebral infarction and diabetes. Other compounds from this series of butyramide derivatives include the following:



Compound	R1	Formula
279244	1-CO ₂ H-cyclohexyl	C ₂₇ H ₃₅ NO ₅
279245	2-CO ₂ H-Ph	C ₂₇ H ₂₉ NO ₅
279246	2-(AcNH ₂ SO ₂)-Ph	C ₂₈ H ₃₂ N ₂ O ₆ S
279247	2-(PhCONH ₂ SO ₂)-Ph	C ₃₃ H ₃₄ N ₂ O ₆ S
279248	2-(BuNHCONH ₂ SO ₂)-Ph	C ₃₁ H ₃₉ N ₃ O ₆ S
279249	2-(1-Pip-CONH ₂ SO ₂)-Ph	C ₃₂ H ₃₉ N ₃ O ₆ S

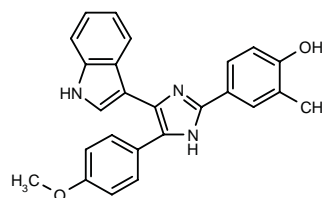
SOURCE – Fujirebio.

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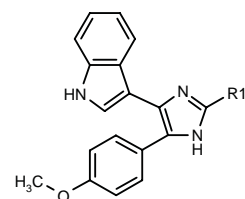
279324

4-[4-(1*H*-Indol-3-yl)-5-(4-methoxyphenyl)-1*H*-imidazol-2-yl]-2-methylphenol



C₂₅ H₂₁ N₃ O₂; Mol wt: 395.4599

ACTION – An inhibitor of Ca²⁺-calmodulin-dependent phosphodiesterase (PDE1; 81% inhibition at 10 μM using enzyme from bovine brain); a representative compound from a series of 4-(3-indolyl)imidazole derivatives, wherein the following are also included:



Compound	R1	Formula
279325	3-Me-Ph	C ₂₅ H ₂₁ N ₃ O
279326	3-OH-Ph	C ₂₄ H ₁₉ N ₃ O ₂
279327	4-OH-Ph	C ₂₄ H ₁₉ N ₃ O ₂
279328	2-OH-Ph	C ₂₄ H ₁₉ N ₃ O ₂
279329	5-Me-2-thienyl	C ₂₃ H ₁₉ N ₃ OS
279330	5-Cl-2-thienyl	C ₂₂ H ₁₆ ClN ₃ OS

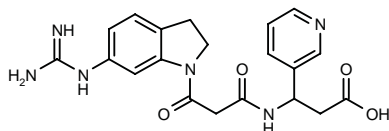
SOURCES – Sagami; Taisho.

REFERENCES

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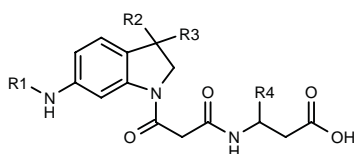
279383

3-[3-(6-Guanidino-2,3-dihydro-1*H*-indol-1-yl)-3-oxopropionamido]-3-(3-pyridinyl)propionic acid



C20 H22 N6 O4; Mol wt: 410.4318

ACTION – Vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist (IC_{50} = 10 nM or less) reported to be useful for inhibiting neovascularization and for preventing restenosis following percutaneous transluminal coronary angioplasty (PTCA). A representative compound from a series of nitrogen-containing heterocycles, wherein the following are also included:



Compound	R1	R2=R3	R4	Formula
279384	CONHCH2Ph	H	3-Pyr	C ₂₇ H ₂₇ N ₅ O ₅
279385	CONHCH2Ph	Me	3-Pyr	C ₂₈ H ₃₁ N ₅ O ₅
279386	cyclopropyl-CH2NHCO	H	3-Pyr	C ₂₄ H ₂₇ N ₅ O ₅
279387	4,5-dihydro-2-imidazolyl	H	3-quinoliny	C ₂₈ H ₂₆ N ₆ O ₄
279388	allyl-NHCO	H	3-Pyr	C ₂₃ H ₂₅ N ₅ O ₅
279390	CONHCH2Ph	H	3-quinoliny	C ₃₁ H ₂₉ N ₅ O ₅
279391	CONHCH2Ph	H	1,3-benzodioxol-5-yl	C ₂₉ H ₂₈ N ₄ O ₇
279392	5,5-(Me)-2-1,4,5,6-tetrahydro-2-pyrimidinyl	H	3-Pyr	C ₂₅ H ₃₀ N ₆ O ₄
279393	3-Pyr-CH2NHC(=NH)	H	3-Pyr	C ₂₈ H ₂₇ N ₇ O ₄
279394	4,5-dihydro-2-imidazolyl	H	3,5-(F)2-Ph	C ₂₃ H ₂₃ F ₂ N ₅ O ₄

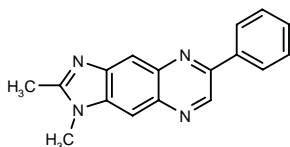
SOURCE – Yamanouchi.

REFERENCES

1. Akamatsu, S. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Nitrogenous heterocyclic derivs.* WO 9933798.

AG-1851**277511**

1,2-Dimethyl-6-phenyl-1*H*-imidazo[4,5-*g*]quinoxaline



C17 H14 N4; Mol wt: 274.3256

ACTION – Potent and selective platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor, a tyrphostin compound found to inhibit PDGF- β receptor tyrosine phosphorylation with an IC_{50} of 5 μ M versus values of 30 μ M for Src kinase and epidermal growth factor (EGF) receptor phosphorylation. It also reversibly inhibited porcine aortic smooth muscle cell growth by 79% at a concentration of 10 μ M, and it inhibited human internal mammary artery smooth muscle cell growth by 54% at a concentration of 25 μ M. Potentially useful in the treatment of proliferative disorders such as restenosis, atherosclerosis, psoriasis, pulmonary fibrosis, glomerulonephritis, rheumatoid arthritis and PDGF receptor-associated malignancies by local or systemic administration.

SOURCE – Yissum.

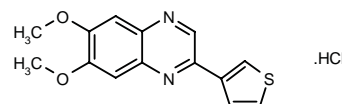
REFERENCES

1. Levitzki, A. et al. (Yissum Research Development Co.) *PDGF receptor kinase inhibitory cpds., their preparation and compns.* WO 9928304.

RPR-101511A***242468**

195239 (as free base)

6,7-Dimethoxy-2-(3-thienyl)quinoxaline hydrochloride



C14 H12 N2 O2 S . HCl; Mol wt: 308.7877

ACTION – Orally active platelet-derived growth factor (PDGF) receptor tyrosine kinase (TK) inhibitor (IC_{50} = 106 nmol/l against human cell-free enzyme), with high selectivity relative to other tyrosine kinases such as epidermal growth factor (EGF) receptor and CSF-1 receptor TKs (IC_{50} > 30,000 nmol/l) and serine/threonine kinases such as protein kinase C (PKC) and protein kinase A (PKA) (IC_{50} > 100,000 nmol/l). Compound was able to inhibit PDGF- β receptor tyrosine kinase autophosphorylation and PDGF-dependent mitogenesis in swine coronary smooth muscle cells (IC_{50} = 220 and 254 nM, respectively), as well as PDGF receptor autophosphorylation and PDGF-dependent chemotaxis and mitogenesis in human aortic smooth muscle cells (IC_{50} = 631, 605 and 492 nM, respectively). In a hypercholesterolemic minipig model of angioplasty-induced coronary artery restenosis, at a dose of 30 mg/kg/day orally for 28 days, it prevented angiographic loss of gain and significantly reduced intimal hyperplasia, independently of an effect on plasma cholesterol and arterial wall accumulation of lipids.

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Spada, A.P. et al. (Rhône-Poulenc Rorer SA) *Bis mono- and bicyclic aryl and heteroaryl cpds. which inhibit EGF and/or PDGF receptor tyrosine kinase.* US 5480883.

2. Spada, A.P. et al. (Rhône-Poulenc Rorer SA) *Bis mono- and bicyclic aryl and heteroaryl cpds. which inhibit EGF and/or PDGF receptor tyrosine kinase.* EP 584222, JP 94507643, US 5409930, WO 9220642.

3. Bilder, G. et al. *Restenosis following angioplasty in the swine coronary artery is inhibited by an orally active PDGF-receptor tyrosine kinase inhibitor, RPR101511A*. *Circulation* 1999, 99(25): 3292.

4. Bilder, G.E. et al. *Angiographic and histologic restenosis following angioplasty in the swine coronary artery is inhibited by an orally active PDGF-receptor tyrosine kinase inhibitor, RPR 101511a*. *Circulation* 1996, 94(8, Suppl.): Abstr 2719.

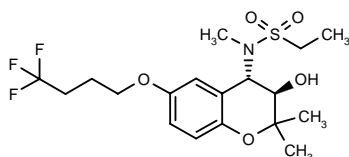
*Identified compound **195239** (see **191796**) Drug Data Rep 1993, 015(06): 0588.

ANTIARRHYTHMIC DRUGS

276294

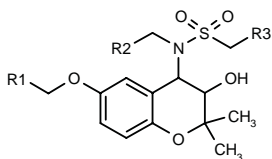
N-[3(*R*)-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]-*N*-methylethanesulfonamide

N-[3(*R*)-Hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-chroman-4(*S*)-yl]-*N*-methylethanesulfonamide



C18 H26 F3 N O5 S; Mol wt: 425.4654

ACTION – Agent for the treatment or prevention of cardiovascular disorders, particularly arrhythmias, as well as gastrointestinal disorders such as ulcers, reflux esophagitis, and diarrhea, a potassium channel blocker acting on cAMP-dependent potassium channels. Compound exhibited an IC₅₀ value of 0.1 μM for inhibition of human I_{Ks} channels expressed in *Xenopus* oocytes. Other compounds from this series of substituted sulfonamide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
276295	Ph	H	H	(±)-trans	C ₂₀ H ₂₅ NO ₅ S
276296	Pr	H	H	(±)-trans	C ₁₇ H ₂₇ NO ₅ S
276297	Ph	Pr	H	(±)-trans	C ₂₃ H ₃₁ NO ₅ S
276298	CH ₂ CH ₂ CF ₃	H	H	(±)-trans	C ₁₇ H ₂₄ F ₃ NO ₅ S
276299	Pr	Me	H	(±)-trans	C ₁₈ H ₂₉ NO ₅ S
276300	Pr	H	H	(-)-(3 <i>S</i> ,4 <i>R</i>)	C ₁₇ H ₂₇ NO ₅ S
276301	Ph	H	Me	(-)-(3 <i>S</i> ,4 <i>R</i>)	C ₂₁ H ₂₇ NO ₅ S
276302	CH ₂ CH ₂ CF ₃	H	H	(+)-(3 <i>R</i> ,4 <i>S</i>)	C ₁₇ H ₂₄ F ₃ NO ₅ S
276303	CH ₂ CH ₂ CF ₃	H	H	(-)-(3 <i>S</i> ,4 <i>R</i>)	C ₁₇ H ₂₄ F ₃ NO ₅ S

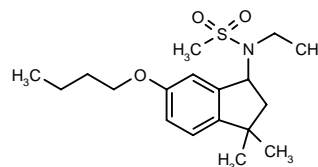
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulphonamide subst. benzopyran derivs., process of preparation, their use as medicines and pharmaceutical compsns. containing them*. CA 2252733, EP 913396, JP 99222485.

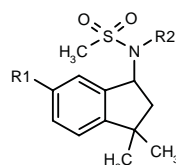
276836

N-(6-Butoxy-3,3-dimethylindan-1-yl)-*N*-ethylmethanesulfonamide



C18 H29 N O3 S; Mol wt: 339.4971

ACTION – Agent for the treatment or prevention of cardiovascular disorders, particularly arrhythmias, as well as gastrointestinal disorders such as ulcers, reflux esophagitis and diarrhea, a potassium channel blocker acting on cAMP-dependent potassium channels. Compound exhibited an IC₅₀ value of 0.44 μM for inhibition of human I_{Ks} channels expressed in *Xenopus* oocytes. Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	Formula
276837	NO ₂	Bu	C ₁₈ H ₂₄ N ₂ O ₄ S
276838	NO ₂	4-Pyr-CH ₂	C ₁₈ H ₂₁ N ₃ O ₄ S
276839	OBu	Me	C ₁₇ H ₂₇ NO ₃ S

SOURCE – Hoechst Marion Roussel.

REFERENCES

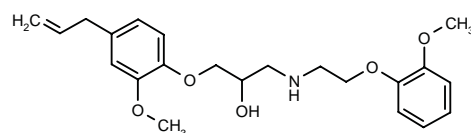
1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulfonamide subst. fused five-membered ring cpds., their use as medicaments as well as pharmaceutical compsns. containing them*. CA 2253211, DE 19749453, EP 915087, JP 99236368.

HEART FAILURE THERAPY

EUGENODIOL

278533

3-(4-Allyl-2-methoxyphenoxy)-1-[2-(2-methoxyphenoxy)-ethylamino]propan-2-ol



C22 H29 N O5; Mol wt: 387.4731

ACTION – Potent and non-subtype-selective β -adrenoceptor antagonist with vasorelaxant properties; it exhibited nanomolar affinity for β_1 - and β_2 -adrenoceptors ($K_i = 9.72$ and 48.29 nM, respectively), as well as for α_1 -adrenoceptors ($K_i = 38.72$ nM). *In vitro* in functional assays, compound was able to antagonize both β_1 - and β_2 -adrenoceptor-mediated effects, as demonstrated by blockade of isoproterenol-induced positive inotropic and chronotropic effects in guinea pig atria (β_1 -adrenoceptor-mediated effect; $pA_2 = 7.88$ and 7.52 , respectively) and isoproterenol-induced relaxation in guinea pig trachea (β_2 -adrenoceptor-mediated effect; $pA_2 = 7.33$). Compound also showed α_1 -adrenoceptor-blocking activity in rat thoracic aorta ($pA_2 = 7.05$ against phenylephrine-induced contractions). *In vivo*, dose-dependent (0.5 , 1.0 and 1.5 mg/kg i.v.) reductions in both blood pressure and heart rate were obtained in anesthetized rats, and it attenuated isoproterenol-induced tachycardia in mecamylamine-treated rats and the phenylephrine-induced pressor response in reserpine-treated rats. Potentially useful for the treatment of chronic heart failure.

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

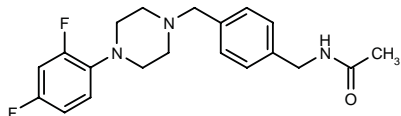
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- Huang, Y.-C. et al. Eugenodilol: A third-generation beta-adrenoceptor blocker, derived from eugenol, with α -adrenoceptor blocking and β_2 -adrenoceptor agonist-associated vasorelaxant activities. J Cardiovasc Pharmacol 1999, 34(1): 10.

TREATMENT OF SHOCK

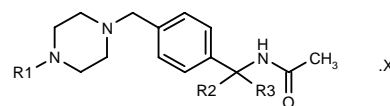
277215

N-[4-[4-(2,4-Difluorophenyl)piperazin-1-ylmethyl]benzyl]-acetamide



C20 H23 F2 N3 O; Mol wt: 359.4177

ACTION – Tumor necrosis factor (TNF- α) production inhibitor and IL-10 production enhancer, as demonstrated in lipopolysaccharide (LPS)-treated mice where it decreased TNF- α production by 17% and increased IL-10 production by 770% following oral administration. It significantly reduced the mortality rate in a murine model of LPS-induced endotoxic shock: only 1 of 9 animals treated orally with the test compound died compared to all 9 untreated mice. Potentially useful for the treatment of acute and chronic inflammatory disorders, autoimmune diseases, allergic disorders and other TNF- α -mediated conditions. Other exemplified piperazine compounds are:



Compound	R1	R2	R3	X	Formula
277216	4-F-Ph	H	Me		C ₂₁ H ₂₆ FN ₃ O
277217	4-F-Ph	Me	Me		C ₂₂ H ₂₈ FN ₃ O
277218	Ph	H	Me	2HCl	C ₂₁ H ₂₇ N ₃ O.2HCl
277219	2-pyrimidinyl	H	H		C ₁₈ H ₂₃ N ₅ O
277220	2-thiazolyl	H	H	HCl	C ₁₇ H ₂₂ N ₄ OS.HCl
277221	2-Pyr	H	H		C ₁₉ H ₂₄ N ₄ O

SOURCE – Yoshitomi.

REFERENCES

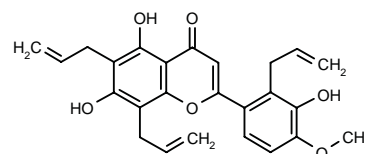
- Adachi, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) Piperazine cpds. and medicinal use thereof. WO 9919301.

TREATMENT OF PERIPHERAL VASCULAR DISEASE

S-17834*

236355

6,8-Diallyl-2-(2-allyl-3-hydroxy-4-methoxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one



C25 H24 O6; Mol wt: 420.4586

ACTION – Endothelial cell adhesion molecule inhibitor, a diosmetin derivative with activity against P-selectin and VCAM-1 ($IC_{50} = 36$ and 126 μ M, respectively), as well as E-selectin and ICAM-1. Compound reduced histamine-induced leaks in the hamster cheek pouch model and orally administered drug (30 mg/kg) reduced vasodilatation induced by sodium nitroprusside in dogs. Potentially useful for the treatment of venous insufficiency.

SOURCE – Servier.

REFERENCES

- Wierzbicki, M. et al. (ADIR et Cie.) Diosmetin derivs., process for their preparation and pharmaceutical compns. containing them. CA 2161297, EP 709383, FR 2726273, JP 96225563, US 5629339.
- Rupin, A. et al. The diosmetin derivative S 17834 inhibits in vitro leukocyte adhesion to selectins and cellular adhesion molecules. Fundam Clin Pharmacol 1999, 13(2): 272.
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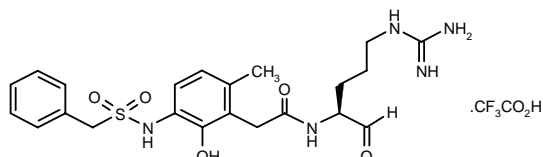
*Identified compound **236355** Drug Data Rep 1996, 018(07): 0616.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

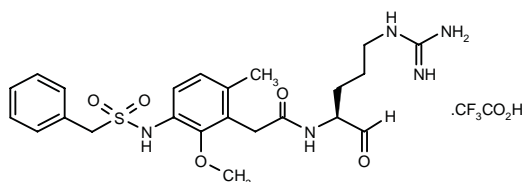
277512

N-[2-[3-(Benzylsulfonamido)-2-hydroxy-6-methylphenyl]-acetyl]-L-argininal trifluoroacetate



C22 H29 N5 O5 S . C2 H F3 O2; Mol wt: 589.5890

ACTION – Antithrombotic agent, a potent and specific thrombin inhibitor with a K_i value for human α -thrombin of 0.79 nM and an IC_{50} value of 3.19 nM, whereas it showed little or no activity against a range of other serine proteases. Another exemplified substituted 3-amino-2-hydroxyphenylacetamide derivative is:



277513: C23 H31 N5 O5 S . C2 H F3 O2

SOURCE – Corvas.

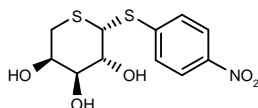
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277545

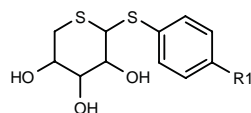
(2*R*,3*R*,4*S*,5*R*)-2-(4-Nitrophenylsulfanyl)tetrahydro-2*H*-thiopyran-3,4,5-triol

1-(4-Nitrophenylsulfanyl)-5-thio- β -L-arabinopyranoside



C11 H13 N O5 S2; Mol wt: 303.3577

ACTION – Orally active anticoagulant, active in a rat venous thrombosis model, where it provided 65% inhibition of thrombus at a dose of 2 mg/kg p.o. Other exemplified compounds within this series of 1,5-dithio-L- and -D-arabinopyranosides include the following:



Compound	R1	Isomer	Formula
277546	NO2	α -L-arabino	C ₁₁ H ₁₃ NO ₅ S ₂
277547	NHAc	β -L-arabino	C ₁₃ H ₁₇ NO ₄ S ₂
277548	CN	β -D-arabino	C ₁₂ H ₁₃ NO ₅ S ₂
277549	NO2	α -D-arabino	C ₁₁ H ₁₃ NO ₅ S ₂
277550	CSNH2	α -D-arabino	C ₁₂ H ₁₅ NO ₃ S ₃

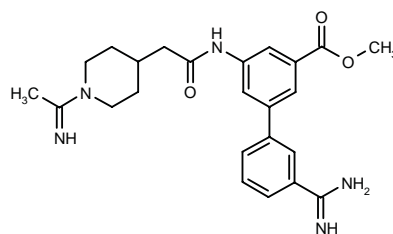
SOURCE – Gedeon Richter.

REFERENCES

1. Kovácsné Bozó, E. et al. (Gedeon Richter Ltd.) *Novel anticoagulant glycosides and pharmaceutical compsns. thereof*. WO 9928312.

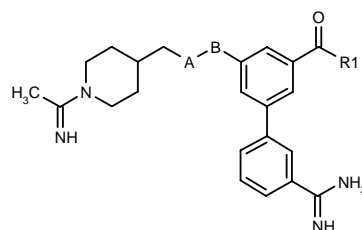
278591

5-[2-[1-(Acetimidoyl)piperidin-4-yl]acetamido]-3'-amidinobiphenyl-3-carboxylic acid methyl ester



C24 H29 N5 O3; Mol wt: 435.5251

ACTION – Anticoagulant and antithrombotic agent, a selective inhibitor of human factor Xa (IC_{50} = 0.1-1 μ M) with no activity against human thrombin (IC_{50} > 100 μ M). Other compounds from this series of biphenylamidino derivatives include the following:



Compound	R1	A	B	Formula
278592	OMe	CH2	NH	C ₂₄ H ₃₁ N ₅ O ₂
278593	OMe	CH2	O	C ₂₄ H ₃₀ N ₄ O ₃
278594	N(Me)2	CH2	O	C ₂₅ H ₃₃ N ₅ O ₂
278596	Me	CH2	O	C ₂₄ H ₃₀ N ₄ O ₂
278597	OEt	CO	NH	C ₂₅ H ₃₁ N ₅ O ₃
278598	OMe	NH	CO	C ₂₄ H ₂₉ N ₅ O ₃
278599	OH	CH2	NH	C ₂₃ H ₂₉ N ₅ O ₂
278600	OH	CH2	O	C ₂₃ H ₂₈ N ₄ O ₃

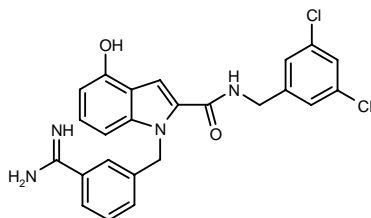
SOURCE – Teijin.

REFERENCES

1. Nakada, K. et al. (Teijin Ltd.) *Biphenylamidino derivs.* JP 99152269.

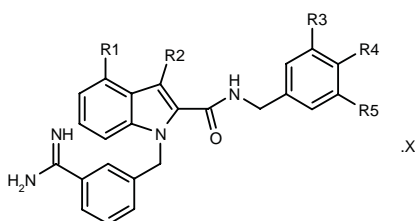
278651

1-(3-Amidinobenzyl)-N-(3,5-dichlorobenzyl)-4-hydroxy-1H-indole-2-carboxamide



C24 H20 Cl2 N4 O2; Mol wt: 467.3540

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of human factor Xa ($K_i = 0.0048 \mu\text{M}$). Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
278652	Me	H	H	N(Me)3+	H	.CF3CO2H .CF3CO2-	$\text{C}_{28}\text{H}_{32}\text{N}_5\text{O}$ $\text{C}_2\text{HF}_3\text{O}_2 \cdot \text{C}_2\text{F}_3\text{O}_2$
278653	OH	H	H	N(Me)3+	H	.CH3CO2H .CH3CO2-	$\text{C}_{27}\text{H}_{30}\text{N}_5\text{O}_2$ $\text{C}_2\text{H}_4\text{O}_2 \cdot \text{C}_2\text{H}_3\text{O}_2$
278654	Me	H	C(=NH)NH2	H	H	2CF3CO2H	$\text{C}_{26}\text{H}_{26}\text{N}_6\text{O}$ $2\text{C}_2\text{HF}_3\text{O}_2$
278655	OH	H	C(=NH)NH2	H	H	2CF3CO2H	$\text{C}_{25}\text{H}_{24}\text{N}_6\text{O}_2$ $2\text{C}_2\text{HF}_3\text{O}_2$
278656	H	Cl	C(=NH)NH2	H	H		$\text{C}_{25}\text{H}_{23}\text{ClN}_6\text{O}$
278657	Me	H	Me	H	Me		$\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}$

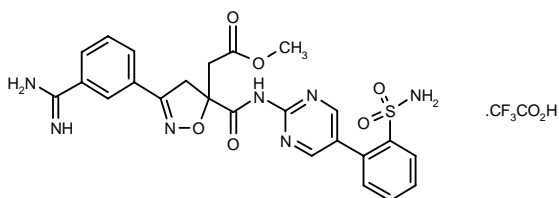
SOURCE – Hoechst Marion Roussel.

REFERENCES

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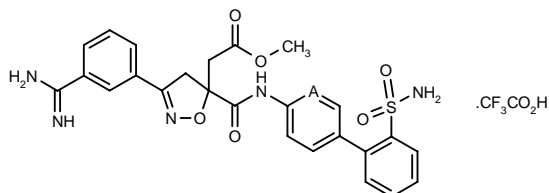
SF-324**279016**

(-)-3-(3-Amidinophenyl)-5-[5-[2-(sulfamoyl)phenyl]-pyrimidin-2-ylcarbonyl]-4,5-dihydroisoxazole-5-acetic acid methyl ester trifluoroacetate



C24 H23 N7 O6 S . C2 H F3 O2; Mol wt: 651.5766

ACTION – Antithrombotic agent, an inhibitor of human factor Xa ($K_i = 2.3 \text{ nM}$) with high selectivity over thrombin and trypsin ($K_i = 8900$ and 170 nM , respectively), as well as against a panel of serine proteases including plasmin, tissue plasminogen activator (tPA), factor VIIa and factor IXa ($K_i = 2500 \text{ nM}$ or more). In the rabbit arteriovenous (AV) shunt model of thrombosis, compound inhibited thrombus weight with an ID_{50} of $0.15 \mu\text{mol/kg/h}$ i.v. Other related isoxazoline derivatives include the following:



Compound	A	Isomer	Formula
279017	CH	(-)	$\text{C}_{26}\text{H}_{25}\text{N}_5\text{O}_6\text{S} \cdot \text{C}_2\text{HF}_3\text{O}_2$
279018	N	(-)	$\text{C}_{25}\text{H}_{24}\text{N}_6\text{O}_6\text{S} \cdot \text{C}_2\text{HF}_3\text{O}_2$

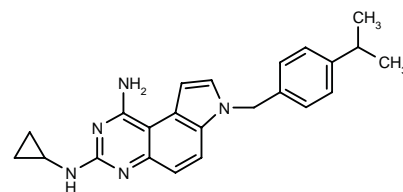
SOURCE – DuPont Pharmaceuticals.

REFERENCES

- Quan, M.L. et al. (The Du Pont Merck Pharmaceutical Co.) *Isoxazoline, isothiazoline and pyrazoline factor Xa inhibitors*. EP 874629, US 5939418, WO 9723212.
- Quan, M.L. et al. *Design and synthesis of isoxazoline derivatives as factor Xa inhibitors*. 1. J Med Chem 1999, 42(15): 2752.
- Quan, M.L. *Design and synthesis of isoxazoline derivatives as factor Xa inhibitors*. 215 th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 202.

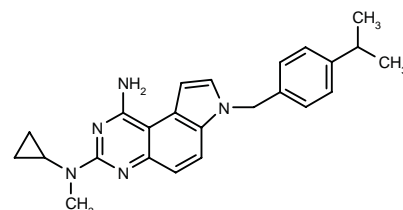
ANTIPLATELET THERAPY**278879**

*N*³-Cyclopropyl-7-(4-isopropylbenzyl)-7H-pyrrolo[3,2-*f*]-quinazoline-1,3-diamine



C23 H25 N5; Mol wt: 371.4855

ACTION – Selective nonpeptide thrombin receptor (PAR-1) antagonist ($\text{IC}_{50} = 56 \text{ nM}$) able to block thrombin-induced platelet aggregation ($\text{IC}_{50} = 3 \mu\text{M}$), but being inactive against ADP-, collagen- or protease-activated thrombin receptor (PAR-4)-induced platelet aggregation. Within this series of pyrroloquinazolines, the following is also included:



278881: C24 H27 N5

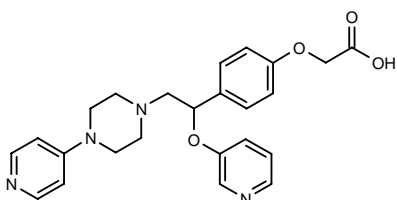
SOURCE – Schering-Plough.

REFERENCES

1. Ahn, H.-S. et al. *Structure-activity relationships of pyrroloquinazolines as thrombin receptor antagonists*. Bioorg Med Chem Lett 1999, 9(14): 2073.

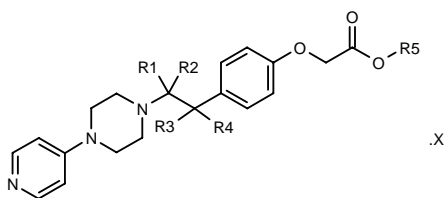
279200

2-[4-[1-(3-Pyridinyloxy)-2-[4-(4-pyridinyl)piperazin-1-yl]ethyl]phenoxy]acetic acid



C24 H26 N4 O4; Mol wt: 434.4934

ACTION – Platelet aggregation inhibitor and antithrombotic agent, a fibrinogen (gpIIb/IIIa) receptor antagonist (IC_{50} = 0.060 μ M) proven to inhibit ADP-induced aggregation of human platelet-rich plasma (PRP) with an IC_{50} of 0.86 μ M and human TxA_2 synthase with an IC_{50} of 0.44 μ M. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
279201	H	H	3-Pyr-O	H	Et		C ₂₆ H ₃₀ N ₄ O ₄
279202	H	H	1-imidazolyl-CH2	H	H	HCl	C ₂₃ H ₂₇ N ₅ O ₃ ·HCl
279203	H	H	1-imidazolyl-CH2	H	Et		C ₂₅ H ₃₁ N ₅ O ₃
279204	-O-		-CH(3-Pyr)-	H	H	HCl	C ₂₅ H ₂₄ N ₄ O ₄ ·HCl

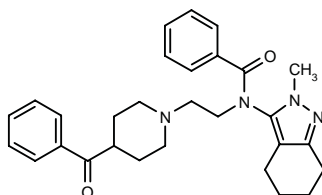
SOURCE – Meiji Seika.

REFERENCES

1. Yamamoto, T. et al. (Meiji Seika Kaisha, Ltd.) *Novel heterocyclic cpds. having antithrombocyte effect*. JP 99171770.

279206

N-[2-(4-Benzoylpiperidin-1-yl)ethyl]-*N*-(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)benzamide



C29 H34 N4 O2; Mol wt: 470.6136

ACTION – Antiplatelet agent, a 5-HT₂ receptor antagonist proven to inhibit collagen-induced aggregation of rabbit platelet-rich plasma with an IC_{50} of 0.026 μ M versus 0.26 μ M for sarpogrelate. A representative condensed heterocyclic compound.

SOURCE – Yoshitomi.

REFERENCES

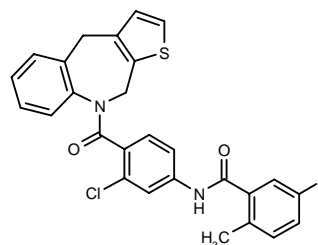
1. Kuroita, T. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Condensed heterocyclic cpds*. JP 99171865.

RENAL-UROLOGIC DRUGS

DIURETICS

278075

N-[3-Chloro-4-(9,10-dihydro-4*H*-thieno[2,3-*c*]benzazepin-9-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide



C27 H20 Cl F N2 O2 S; Mol wt: 490.9840

ACTION – Arginine vasopressin V₂ receptor antagonist (IC_{50} = 6.8 nM) with > 1000-fold selectivity over the V_{1A} receptor. *In vivo* in water-loaded rats, compound (10 mg/kg p.o.) antagonized the antidiuretic effect of AVP. Potentially useful for the treatment of fluid retention in pathologies such as congestive heart failure, liver cirrhosis, nephrotic syndrome, CNS injuries, lung disease and hyponatremia.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Albright, J.D. and Du, X. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5736538.

2. Albright, J.D. et al. (American Cyanamid Co.) *N-Acylated tricyclic azaheterorings useful as vasopressin antagonists*. CA 2128955, EP 640592, JP 95179430, US 5512563, WO 9747624.

3. Aranapakam, V. et al. *4,10-Dihydro-5H-thieno[3,2-*c*][1]benzazepine derivatives and 9,10-dihydro-4H-thieno[2,3-*c*][1]benzazepine derivatives as orally active arginine vasopressin receptor antagonists*. Bioorg Med Chem Lett 1999, 9(13): 1733.

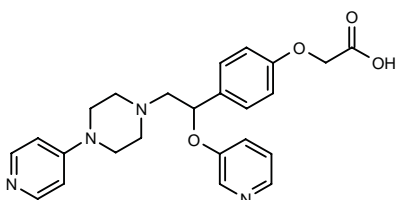
SOURCE – Schering-Plough.

REFERENCES

1. Ahn, H.-S. et al. *Structure-activity relationships of pyrroloquinazolines as thrombin receptor antagonists*. Bioorg Med Chem Lett 1999, 9(14): 2073.

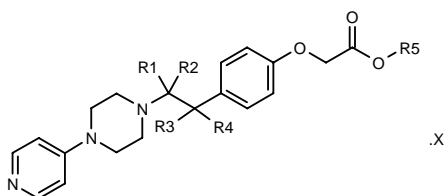
279200

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C24 H26 N4 O4; Mol wt: 434.4934

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Compound	R1	R2	R3	R4	R5	X	Formula
279201	H	H	3-Pyr-O	H	Et		C ₂₆ H ₃₀ N ₄ O ₄
279202	H	H	1-imidazolyl-CH ₂	H	H	HCl	C ₂₃ H ₂₇ N ₅ O ₃ ·HCl
279203	H	H	1-imidazolyl-CH ₂	H	Et		C ₂₅ H ₃₁ N ₅ O ₃
279204	-O-		-CH(3-Pyr)-	H	HCl		C ₂₅ H ₂₄ N ₄ O ₄ ·HCl

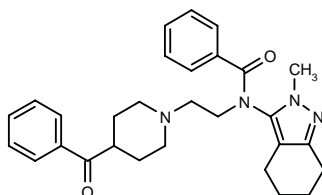
SOURCE – Meiji Seika.

REFERENCES

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279206

N-[2-(4-Benzoylpiperidin-1-yl)ethyl]-*N*-(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)benzamide



C29 H34 N4 O2; Mol wt: 470.6136

ACTION – Antiplatelet agent, a 5-HT₂ receptor antagonist proven to inhibit collagen-induced aggregation of rabbit platelet-rich plasma with an IC_{50} of 0.026 μ M versus 0.26 μ M for sarpogrelate. A representative condensed heterocyclic compound.

SOURCE – Yoshitomi.

REFERENCES

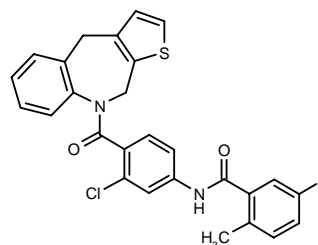
1. Kuroita, T. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Condensed heterocyclic cpds*. JP 99171865.

RENAL-UROLOGIC DRUGS

DIURETICS

278075

N-[3-Chloro-4-(9,10-dihydro-4*H*-thieno[2,3-*c*]benzazepin-9-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide



C27 H20 Cl F N2 O2 S; Mol wt: 490.9840

ACTION – Arginine vasopressin V₂ receptor antagonist (IC_{50} = 6.8 nM) with > 1000-fold selectivity over the V_{1A} receptor. *In vivo* in water-loaded rats, compound (10 mg/kg p.o.) antagonized the antidiuretic effect of AVP. Potentially useful for the treatment of fluid retention in pathologies such as congestive heart failure, liver cirrhosis, nephrotic syndrome, CNS injuries, lung disease and hyponatremia.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Albright, J.D. and Du, X. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5736538.

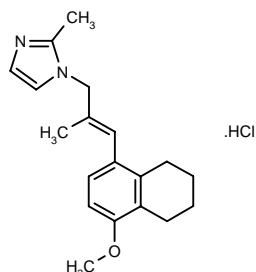
2. Albright, J.D. et al. (American Cyanamid Co.) *N-Acylated tricyclic azaheterorings useful as vasopressin antagonists*. CA 2128955, EP 640592, JP 95179430, US 5512563, WO 9747624.

3. Aranapakam, V. et al. *4,10-Dihydro-5H-thieno[3,2-*c*][1]benzazepine derivatives and 9,10-dihydro-4H-thieno[2,3-*c*][1]benzazepine derivatives as orally active arginine vasopressin receptor antagonists*. Bioorg Med Chem Lett 1999, 9(13): 1733.

TREATMENT OF URINARY INCONTINENCE

277505

(*E*)-1-(4-Methoxy-5,6,7,8-tetrahydro-1-naphthyl)-2-methyl-3-(2-methyl-1*H*-imidazol-1-yl)-1-propene hydrochloride



C₁₉ H₂₄ N₂ O . HCl; Mol wt: 332.8725

ACTION – Compound useful for preventing frequent urination or urinary incontinence, proven to be more effective than propiverine or flavoxate in the rat rhythmic bladder contraction model.

SOURCE – Nippon Kayaku.

REFERENCES

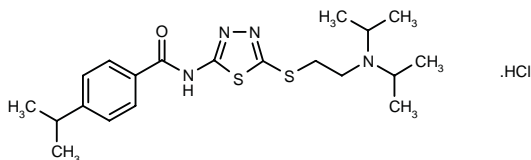
1. Koga, I. et al. (Nippon Kayaku Co., Ltd.) *Heterocyclic cpds. and use thereof*. WO 9921839.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

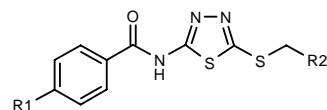
277429

N-[5-[2-(*N,N*-Diisopropylamino)ethylsulfanyl]-1,3,4-thiadiazol-2-yl]-4-isopropylbenzamide hydrochloride

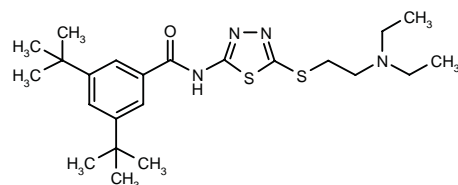


C₂₀ H₃₀ N₄ O S₂ . HCl; Mol wt: 443.0769

ACTION – Antiulcer agent proven active *in vivo* against restraint-water immersion stress-induced ulcers in rats (96% inhibition at 100 mg/kg p.o.) and to exert marked gastric antiseecretory activity *in vitro* in rabbit gastric fundus gland preparations (104% inhibition at 10 μM). Compound exhibited no cytotoxic effects in rabbit gastric corpus mucosa homogenates at a concentration of 100 μM. Within this series of thiadiazoleamide derivatives, the following are also included:



Compound	R1	R2	Formula
277430	i-Pr	CH ₂ N(Et) ₂	C ₁₈ H ₂₆ N ₄ O S ₂
277431	i-Pr	CH ₂ N(i-Pr) ₂	C ₂₀ H ₃₀ N ₄ O S ₂
277432	t-Bu	CH ₂ N(Et) ₂	C ₁₉ H ₂₈ N ₄ O S ₂
277433	t-Bu	CH ₂ N(i-Pr) ₂	C ₂₁ H ₃₂ N ₄ O S ₂
277435	i-PrO	CH ₂ N(Et) ₂	C ₁₈ H ₂₆ N ₄ O ₂ S ₂
277436	t-BuO	CH ₂ N(Et) ₂	C ₁₉ H ₂₈ N ₄ O ₂ S ₂
277437	t-BuNH	CH ₂ N(Et) ₂	C ₁₉ H ₂₉ N ₅ O S ₂
277438	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	CH ₂ N(Et) ₂	C ₂₅ H ₃₆ N ₄ O ₂ S ₂
277439	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	CH ₂ CH ₂ N(Et) ₂	C ₂₆ H ₃₈ N ₄ O ₂ S ₂
277440	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	1-Pip-CH ₂	C ₂₆ H ₃₆ N ₄ O ₂ S ₂
277441	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	1-Pip-CH ₂ CH ₂	C ₂₇ H ₃₈ N ₄ O ₂ S ₂
277442	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	2-Pyr	C ₂₅ H ₂₈ N ₄ O ₂ S ₂
277443	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Me	C ₂₁ H ₂₇ N ₃ O ₂ S ₂
277444	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Et	C ₂₂ H ₂₉ N ₃ O ₂ S ₂
277445	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	i-Pr	C ₂₃ H ₃₁ N ₃ O ₂ S ₂
277446	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Ph	C ₂₆ H ₂₉ N ₃ O ₂ S ₂



277434: C₂₃ H₃₆ N₄ O S₂

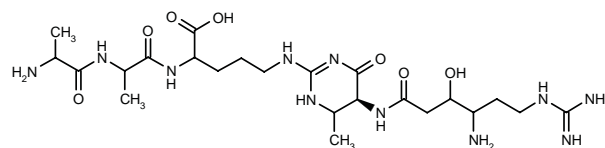
SOURCE – Shiseido.

REFERENCES

1. Nishino, C. et al. (Shiseido Co. Ltd.) *Thiadiazoleamide deriv. and anti-ulcer drug*. US 5912258.

277503

*N*²-(DL-Alanyl-DL-alanyl)-*N*⁵-[5-(4-amino-6-guanidino-3-hydroxyhexanamido)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrimidin-2-yl]-DL-ornithine isomer A

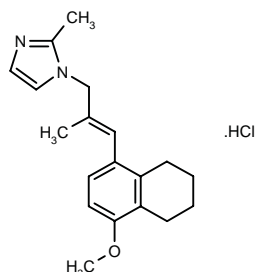


C₂₃ H₄₃ N₁₁ O₇; Mol wt: 585.6627

TREATMENT OF URINARY INCONTINENCE

277505

(*E*)-1-(4-Methoxy-5,6,7,8-tetrahydro-1-naphthyl)-2-methyl-3-(2-methyl-1*H*-imidazol-1-yl)-1-propene hydrochloride



C₁₉ H₂₄ N₂ O . HCl; Mol wt: 332.8725

ACTION – Compound useful for preventing frequent urination or urinary incontinence, proven to be more effective than propiverine or flavoxate in the rat rhythmic bladder contraction model.

SOURCE – Nippon Kayaku.

REFERENCES

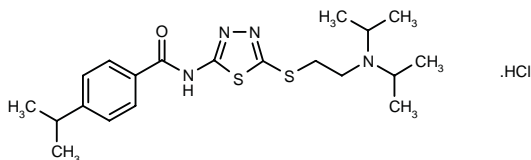
1. Koga, I. et al. (Nippon Kayaku Co., Ltd.) *Heterocyclic cpds. and use thereof*. WO 9921839.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

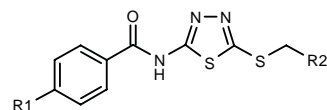
277429

N-[5-[2-(*N,N*-Diisopropylamino)ethylsulfanyl]-1,3,4-thiadiazol-2-yl]-4-isopropylbenzamide hydrochloride

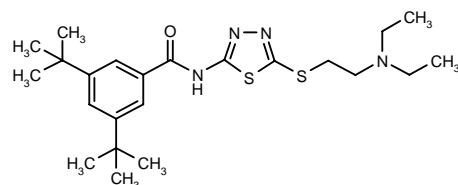


C₂₀ H₃₀ N₄ O S₂ . HCl; Mol wt: 443.0769

ACTION – Antiulcer agent proven active *in vivo* against restraint-water immersion stress-induced ulcers in rats (96% inhibition at 100 mg/kg p.o.) and to exert marked gastric antiseecretory activity *in vitro* in rabbit gastric fundus gland preparations (104% inhibition at 10 μM). Compound exhibited no cytotoxic effects in rabbit gastric corpus mucosa homogenates at a concentration of 100 μM. Within this series of thiadiazoleamide derivatives, the following are also included:



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277432	t-Bu	CH ₂ N(Et) ₂	C ₁₉ H ₂₈ N ₄ O S ₂
277433	t-Bu	CH ₂ N(i-Pr) ₂	C ₂₁ H ₃₂ N ₄ O S ₂
277435	i-PrO	CH ₂ N(Et) ₂	C ₁₈ H ₂₆ N ₄ O ₂ S ₂
277436	t-BuO	CH ₂ N(Et) ₂	C ₁₉ H ₂₈ N ₄ O ₂ S ₂
277437	t-BuNH	CH ₂ N(Et) ₂	C ₁₉ H ₂₉ N ₅ O S ₂
277438	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	CH ₂ N(Et) ₂	C ₂₅ H ₃₆ N ₄ O ₂ S ₂
277439	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	CH ₂ CH ₂ N(Et) ₂	C ₂₆ H ₃₈ N ₄ O ₂ S ₂
277440	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	1-Pip-CH ₂	C ₂₆ H ₃₆ N ₄ O ₂ S ₂
277441	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	1-Pip-CH ₂ CH ₂	C ₂₇ H ₃₈ N ₄ O ₂ S ₂
277442	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	2-Pyr	C ₂₅ H ₂₈ N ₄ O ₂ S ₂
277443	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Me	C ₂₁ H ₂₇ N ₃ O ₂ S ₂
277444	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Et	C ₂₂ H ₂₉ N ₃ O ₂ S ₂
277445	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	i-Pr	C ₂₃ H ₃₁ N ₃ O ₂ S ₂
277446	OCH ₂ CH=C(Me)CH ₂ -CH ₂ CH=C(Me) ₂	Ph	C ₂₆ H ₂₉ N ₃ O ₂ S ₂



277434: C₂₃ H₃₆ N₄ O S₂

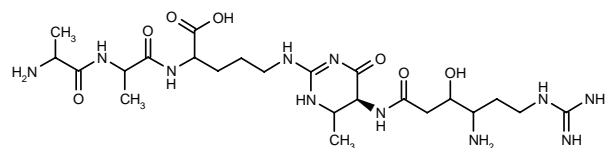
SOURCE – Shiseido.

REFERENCES

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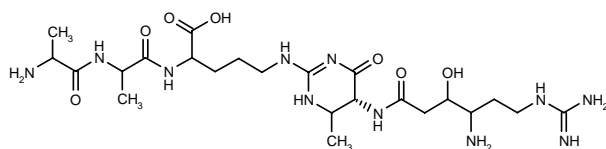
277503

*N*²-(DL-Alanyl-DL-alanyl)-*N*⁵-[5-(4-amino-6-guanidino-3-hydroxyhexanamido)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrimidin-2-yl]-DL-ornithine isomer A



C₂₃ H₄₃ N₁₁ O₇; Mol wt: 585.6627

ACTION – Physiologically active substance produced by *Bacillus lentus* HC-69 (IFO 16114, FERM BP-6144) found to exert anti-*Helicobacter pylori* activity (MIC = 0.4 µg/ml). It significantly reduced gastric bacterial counts in mice infected with *H. pylori* TN2F4 at a dose of 50 mg/kg b.i.d. p.o. for 2 days. Another compound isolated from the same source is:



277504: C23 H43 N11 O7

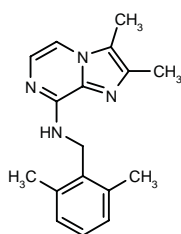
SOURCE – Takeda.

REFERENCES

1. Miyakawa, K. et al. (Takeda Chemical Industries, Ltd.) *Physiologically active substances, their preparation method and agents*. JP 99124368.

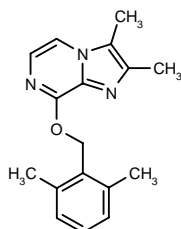
277526

N-(2,6-Dimethylbenzyl)-*N*-(2,3-dimethylimidazo[1,2-*a*]-pyrazin-8-yl)amine



C17 H20 N4; Mol wt: 280.3730

ACTION – Gastric antisecretory agent, an H⁺/K⁺-ATPase inhibitor (IC₅₀ = 0.16 µM in isolated rabbit gastric glands). Potentially useful in the treatment of gastrointestinal inflammatory diseases, as well as conditions involving infection by *Helicobacter pylori* of human gastric mucosa in combination with at least one antimicrobial agent. Another specifically claimed heterocyclic compound is:



277527: C17 H19 N3 O

SOURCE – AstraZeneca.

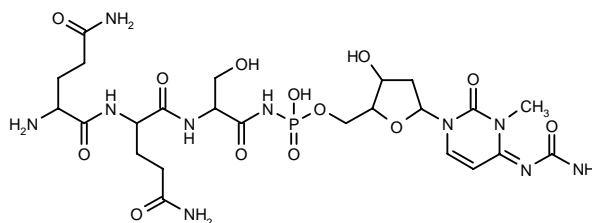
REFERENCES

1. Amin, K. et al. (Astra AB) *Heterocyclic cpds. for inhibition of gastric acid secretion, processes for their preparation and pharmaceutical compns. thereof*. WO 9928322.

HC-62

278581

N-[1-[5-[DL-Glutaminy]-DL-glutaminy]-DL-serylamino-(hydroxy)phosphoryloxymethyl]-4-hydroxytetrahydrofuran-2-yl]-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-ylidene]urea



C24 H39 N10 O13 P; Mol wt: 706.6031

ACTION – Antiulcer agent isolated from a culture of *Bacillus* sp. HC-62 (FERM BP-5929), with potent antibacterial activity against *Helicobacter pylori* (MIC = 0.025 µg/ml against *H. pylori* strain NCTC11637). Activity was also demonstrated *in vivo* in mice infected with *H. pylori* TN2F4, where it produced complete clearance of bacterial infection at 50 mg/kg b.i.d. p.o. x 2 days.

SOURCE – Takeda.

REFERENCES

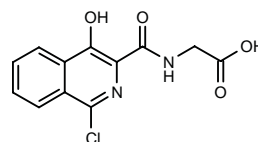
1. Miyakawa, K. et al. (Takeda Chemical Industries, Ltd.) *Physiologically active substances, their preparation method and agents*. JP 99147892.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

276153

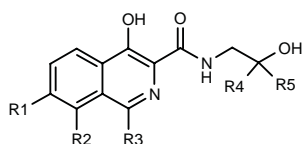
2-(1-Chloro-4-hydroxyisoquinolin-3-ylcarboxamido)acetic acid

N-(1-Chloro-4-hydroxyisoquinolin-3-ylcarbonyl)glycine



C12 H9 Cl N2 O4; Mol wt: 280.6661

ACTION – Antifibrotic agent, a prolyl 4-hydroxylase inhibitor (IC₅₀ = 2.30 M) shown to be active against CCl₄-induced liver fibrosis in rats (67 and 71% inhibition at 20 mg/kg i.p. and 100 mg/kg p.o., respectively). Potentially useful for the treatment of fibrotic diseases of the liver, lungs and skin. Other specifically claimed compounds from this series of substituted isoquinolin-3-carboxamides include the following:



Compound	R1	R2	R3	R4	R5	Formula
276154	H	Cl	H	-O-		C ₁₂ H ₉ ClN ₂ O ₄
276155	i-PrO	H	Cl	-O-		C ₁₅ H ₁₅ ClN ₂ O ₅
276156	i-PrO	H	H	-O-		C ₁₅ H ₁₆ N ₂ O ₅
276157	i-PrO	H	Cl	H	H	C ₁₅ H ₁₇ ClN ₂ O ₄

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Weidmann, K. et al. (Hoechst Marion Roussel Deutschland GmbH) *Substd. isoquinolin-3-carboxyamides, their preparation and medical use*. CA 2250664, CA 2251647, DE 19746287, EP 911340.

TREATMENT OF PANCREATIC DISORDERS

PA153

278188

ACTION – Tissue-specific polypeptide transcribed from pancreatic tissue that it is potentially useful in the detection, diagnosis, staging, monitoring, prognosticating, *in vivo* imaging, prevention and treatment of pancreatic diseases, including pancreatic cancer, as well as for determining the predisposition of an individual to develop diseases or conditions of the pancreas. Antibodies that bind specifically to PA153-encoded polypeptide or protein, as well as agonists or inhibitors that block the actions of PA153, are potentially useful in the treatment of pancreatic diseases, tumors or metastasis.

SOURCE – Abbott.

REFERENCES

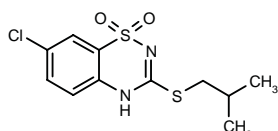
1. Billing-Medel, P.A. et al. (Abbott Laboratories Inc.) *Reagents and methods useful for detecting diseases of the pancreas*. WO 9931274.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

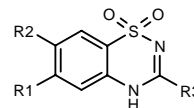
278456

7-Chloro-3-(isobutylsulfanyl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide



C₁₁ H₁₃ Cl N₂ O₂ S₂; Mol wt: 304.8207

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of 1,2,4-benzothiadiazine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
278457	CF ₃	H	i-PrS	C ₁₁ H ₁₁ F ₃ N ₂ O ₂ S ₂
278458	F	H	i-PrO	C ₁₀ H ₁₁ FN ₂ O ₃ S
278459	Br	H	i-PrO	C ₁₀ H ₁₁ BrN ₂ O ₃ S
278460	H	Me	cyclobutyl-S	C ₁₂ H ₁₄ N ₂ O ₄ S ₂

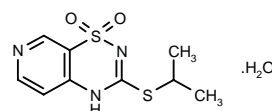
SOURCE – Novo Nordisk.

REFERENCES

1. De Tullio, P. et al. (Novo Nordisk A/S) *1,2,4-Benzothiadiazine derivs., their preparation and use*. WO 9932467.

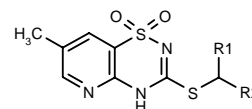
278477

3-(Isopropylsulfanyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide hydrate



C₉ H₁₁ N₃ O₂ S₂ · H₂O; Mol wt: 275.3517

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of pyrido[1,2,4]thiadiazine derivatives, the following are also specifically claimed:

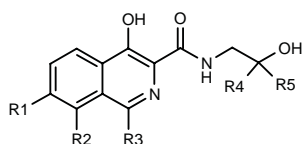


Compound	R1	R2	Formula
278478	Me	Me	C ₁₀ H ₁₃ N ₃ O ₂ S ₂
278479	cyclopropyl	H	C ₁₁ H ₁₃ N ₃ O ₂ S ₂

SOURCE – Novo Nordisk.

REFERENCES

1. De Tullio, P. et al. (Novo Nordisk A/S) *Pyrido 1,2,4-thiadiazine derivs., their preparation and use*. WO 9932495.



Compound	R1	R2	R3	R4	R5	Formula
276154	H	Cl	H	-O-		C ₁₂ H ₉ ClN ₂ O ₄
276155	i-PrO	H	Cl	-O-		C ₁₅ H ₁₅ ClN ₂ O ₅
276156	i-PrO	H	H	-O-		C ₁₅ H ₁₆ N ₂ O ₅
276157	i-PrO	H	Cl	H	H	C ₁₅ H ₁₇ ClN ₂ O ₄

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Weidmann, K. et al. (Hoechst Marion Roussel Deutschland GmbH) *Substd. isoquinolin-3-carboxyamides, their preparation and medical use*. CA 2250664, CA 2251647, DE 19746287, EP 911340.

TREATMENT OF PANCREATIC DISORDERS

PA153

278188

ACTION – Tissue-specific polypeptide transcribed from pancreatic tissue that it is potentially useful in the detection, diagnosis, staging, monitoring, prognosticating, *in vivo* imaging, prevention and treatment of pancreatic diseases, including pancreatic cancer, as well as for determining the predisposition of an individual to develop diseases or conditions of the pancreas. Antibodies that bind specifically to PA153-encoded polypeptide or protein, as well as agonists or inhibitors that block the actions of PA153, are potentially useful in the treatment of pancreatic diseases, tumors or metastasis.

SOURCE – Abbott.

REFERENCES

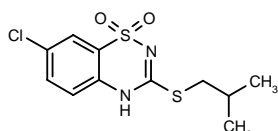
1. Billing-Medel, P.A. et al. (Abbott Laboratories Inc.) *Reagents and methods useful for detecting diseases of the pancreas*. WO 9931274.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

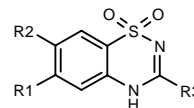
278456

7-Chloro-3-(isobutylsulfanyl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide



C₁₁ H₁₃ Cl N₂ O₂ S₂; Mol wt: 304.8207

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of 1,2,4-benzothiadiazine derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
278457	CF ₃	H	i-PrS	C ₁₁ H ₁₁ F ₃ N ₂ O ₂ S ₂
278458	F	H	i-PrO	C ₁₀ H ₁₁ FN ₂ O ₃ S
278459	Br	H	i-PrO	C ₁₀ H ₁₁ BrN ₂ O ₃ S
278460	H	Me	cyclobutyl-S	C ₁₂ H ₁₄ N ₂ O ₄ S ₂

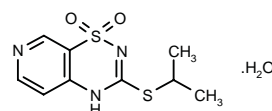
SOURCE – Novo Nordisk.

REFERENCES

1. De Tullio, P. et al. (Novo Nordisk A/S) *1,2,4-Benzothiadiazine derivs., their preparation and use*. WO 9932467.

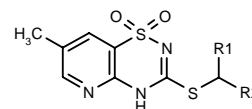
278477

3-(Isopropylsulfanyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide hydrate



C₉ H₁₁ N₃ O₂ S₂ · H₂O; Mol wt: 275.3517

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by modulating ATP-sensitive potassium (K_{ATP}) channels. Within this series of pyrido[1,2,4]thiadiazine derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
278478	Me	Me	C ₁₀ H ₁₃ N ₃ O ₂ S ₂
278479	cyclopropyl	H	C ₁₁ H ₁₃ N ₃ O ₂ S ₂

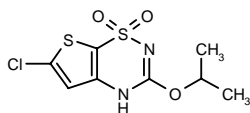
SOURCE – Novo Nordisk.

REFERENCES

1. De Tullio, P. et al. (Novo Nordisk A/S) *Pyrido 1,2,4-thiadiazine derivs., their preparation and use*. WO 9932495.

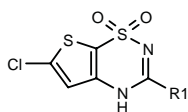
278565

6-Chloro-3-isopropoxy-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide



C₈H₉ClN₂O₃S₂; Mol wt: 280.7551

ACTION – Agent for the treatment of endocrine, cardiovascular, pulmonary, gastrointestinal, urogenital and CNS disorders, particularly hyperinsulinemia and diabetes, that acts by opening ATP-sensitive potassium (K_{ATP}) channels. Other exemplified compounds within this series of fused 1,2,4-thiadiazines include the following:



Compound	R1	Formula
278566	cyclopentyl-O	C ₁₀ H ₁₁ ClN ₂ O ₃ S ₂
278567	cyclopropyl-CH ₂ S	C ₉ H ₉ ClN ₂ O ₂ S ₃
278568	EtS	C ₇ H ₇ ClN ₂ O ₂ S ₃
278569	i-PrS	C ₈ H ₉ ClN ₂ O ₂ S ₃
278570	PrS	C ₈ H ₉ ClN ₂ O ₂ S ₃
278571	cyclopentyl-S	C ₁₀ H ₁₁ ClN ₂ O ₂ S ₃
278572	SCH(Me)Et	C ₉ H ₁₁ ClN ₂ O ₂ S ₃
278573	i-BuS	C ₉ H ₁₁ ClN ₂ O ₂ S ₃
278574	SOPr	C ₈ H ₉ ClN ₂ O ₃ S ₃
278575	OMe	C ₆ H ₅ ClN ₂ O ₃ S ₂

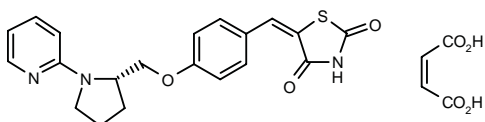
SOURCE – Novo Nordisk.

REFERENCES

- Nielsen, F.E. et al. (Novo Nordisk A/S) *Fused 1,2,4-thiadiazine derivs., their preparation and use.* WO 9932494.

278887

(*E*)-5-[4-[1-(2-Pyridinyl)pyrrolidin-2(*S*)-ylmethoxy]-benzylidene]thiazolidine-2,4-dione maleate



C₂₀H₁₉N₃O₃S; C₄H₄O₄; Mol wt: 497.5257

M.p. 132 °C, $[\alpha]_D^{27}$ – 77.3° (c 1.0, DMSO).

ACTION – Potent euglycemic and hypolipidemic agent, a thiazolidinedione analogue that is able to dose-dependently (3-30 mg/kg p.o for 6 days) reduce plasma glucose and triglyceride levels in *db/db* mice, with a maximal reduction of 63.6 and 71.25%, respectively, at 30 mg/kg p.o., and in *ob/ob* mice, with maximal reductions of 73.00 and 68.50%, respectively, at 30 mg/kg p.o. for 14 days. Compound also improved glucose tolerance in both types of mice. Compound had no significant activity in transactivation studies of peroxisome proliferator-activated receptor subtypes (PPAR γ , PPAR α). Potentially useful for the treatment of type II diabetes.

SOURCE – Dr. Reddy's Research Foundation.

REFERENCES

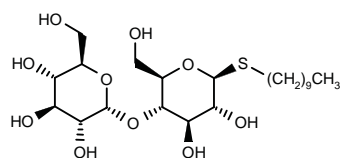
- Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Heterocyclic cpds. having antidiabetic, hypolipidaemic, antihypertensive properties, process for their preparation and pharmaceutical compsns. containing them.* US 5919782.
- Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Thiazolidinedione cpds. having antidiabetic, hypolipidaemic, antihypertensive properties, process for their preparation and pharmaceutical compsns. thereof.* WO 9741120.
- Lohray, B.B. et al. *Novel euglycemic and hypolipidemic agents. 4. Pyridyl- and quinolinyl-containing thiazolidinediones.* J Med Chem 1999, 42(14): 2569.
- Vikramadithyan, R.K. et al. *A weak PPAR γ activating thiazolidinedione with potent antidiabetic and hypolipidemia activities.* Diabetologia 1999, 42(Suppl. 1): Abstr 860.

DecbSM

277262

Decyl 4-*O*- α -D-glucopyranosyl-1-thio- β -D-glucopyranoside

Decyl β -D-thiomaltoside



C₂₂H₄₂O₁₀S; Mol wt: 498.6298

ACTION – Hypoglycemic agent able to increase glucose disposal into glycogen, improve glucose tolerance and induce significant and sustained reductions in blood glucose levels following oral administration to *ob/ob* mice, without apparent toxicity. Potentially useful for the treatment of type II diabetes.

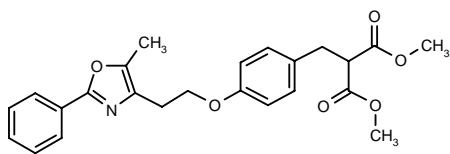
SOURCE – University of Alabama, Birmingham, AL (US).

REFERENCES

- Meezan, E. and Meezan, E.M. *Decyl-beta-D-thiomaltoside is an artificial glycogen primer with hypoglycemic activity.* Diabetes 1999, 48(Suppl. 1): Abstr 1223.

JTP-20993***265286**

2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-malonic acid dimethyl diester



C24 H25 N O6; Mol wt: 423.4625

Colorless solid, m.p. 87.9-8.5 °C.

ACTION – Antidiabetic agent, an insulin sensitizer able to enhance insulin-induced triglyceride accumulation in 3T3-L1 cells ($EC_{50} = 0.059$ nM) and to decrease plasma glucose levels ($ED_{50} = 0.17$ mg/kg/day p.o. for 4 days) in genetically diabetic KKA^y mice, selected as a successor to JTT-501.

SOURCE – Japan Tobacco.**REFERENCES**

1. Shinkai, H. (Japan Tobacco Inc.) *Isoxazolidinedione deriv. and use thereof*. EP 684242, JP 96517913, US 5728720, WO 9518125.

2. Shinkai, H. et al. (Japan Tobacco Inc.) *Propionic acid derivs. and applications thereof*. EP 930299, WO 9807699.

3. Shinkai, H. et al. *Isoxazolidine-3,5-dione and noncyclic 1,3-dicarbonyl compounds as hypoglycemic agents*. J Med Chem 1998, 41(11): 1927.

MONOGRAPH – Shinkai, H. *The isoxazolidine-3,5-dione hypoglycemic agent JTT-501 and other nonthiazolidinedione insulin sensitizers*. Drugs Fut 1999, 24(8): 0893.

*Identified compound **265286** Drug Data Rep 1998, 020(08): 0690.

SULPHOSTIN**279223**

ACTION – Potent inhibitor of dipeptidyl peptidase IV (82% inhibition at 0.05 µg/ml using enzyme from rat renal homogenates) isolated from a culture of *Streptomyces* sp. MK251-43F3 (FERM BP-6571).

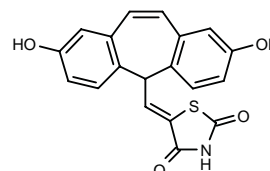
SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Novel physiologically active substance sulphostin, process for producing the same, and use thereof*. WO 9925719.

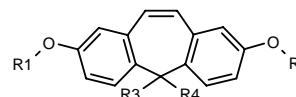
TREATMENT OF DIABETIC COMPLICATIONS**277520**

5-[(Z)-2,8-Dihydroxy-5H-dibenzo[a,d]cyclohepten-5-ylmethylene]thiazolidine-2,4-dione



C19 H13 N O4 S; Mol wt: 351.3807

ACTION – Aldose reductase inhibitor ($IC_{50} = 1.25$ µM) considered to have potential in the treatment of diabetic complications. Other exemplified dibenzocycloheptenone derivatives include the following:



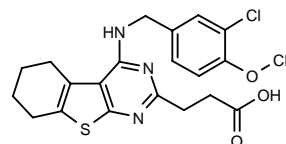
Compound	R1=R2	R3	R4	Formula
277521	H	-O-		C ₁₅ H ₁₀ O ₃
277522	H	-CONHCOCH2-		C ₁₈ H ₁₃ NO ₄
277523	Me	(Z)-2,4-dioxo-5-thiazolidinylidene=CH		C ₂₁ H ₁₇ NO ₄ S

SOURCE – Senju.**REFERENCES**

1. Inoue, J. and Sai, O. (Senju Pharmaceuticals Co., Ltd.) *Dibenzocycloheptenone derivs. and their salts*. JP 99130713.

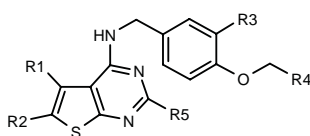
TREATMENT OF MALE SEXUAL DYSFUNCTION**277530**

3-[4-(3-Chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid



C21 H22 Cl N3 O3 S; Mol wt: 431.9418

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor expected to be useful in the treatment of impotence and cardiovascular disorders. Other specifically claimed thienopyrimidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
277531	-(CH ₂) ₄ -		-O-		(CH ₂) ₃ CO ₂ H	C ₂₂ H ₂₃ N ₃ O ₄ S
277532	-(CH ₂) ₄ -		-O-		(CH ₂) ₆ CO ₂ H	C ₂₆ H ₂₉ N ₃ O ₄ S
277533	-(CH ₂) ₄ -		Cl	H	(CH ₂) ₆ CO ₂ H	C ₂₅ H ₃₀ ClN ₃ O ₃ S
277534	-(CH ₂) ₄ -		Cl	H	(CH ₂) ₄ CO ₂ H	C ₂₃ H ₂₆ ClN ₃ O ₃ S
277535	H	Me	Cl	H	(CH ₂) ₄ CO ₂ H	C ₂₀ H ₂₂ ClN ₃ O ₃ S
277536	H	Me	Cl	H	(CH ₂) ₃ CO ₂ H	C ₁₉ H ₂₀ ClN ₃ O ₃ S
277537	H	Me	-O-		(CH ₂) ₃ CO ₂ H	C ₁₉ H ₁₉ N ₃ O ₄ S
277538	-(CH ₂) ₄ -		Cl	H	4-(CH ₂ CO ₂ H)-cyclohexyl	C ₂₆ H ₃₀ ClN ₃ O ₃ S
277539	H	Me	-O-		(CH ₂) ₄ CO ₂ H	C ₂₀ H ₂₁ N ₃ O ₄ S

SOURCE – Merck KGaA.

REFERENCES

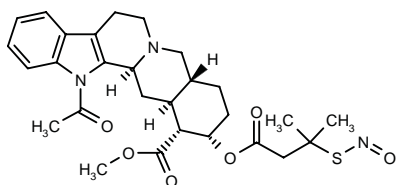
1. Jonas, R. et al. (Merck Patent GmbH) *Thienopyrimidines*. DE 19752952, WO 9928325.

NMI-187^{1,3-5}

243597

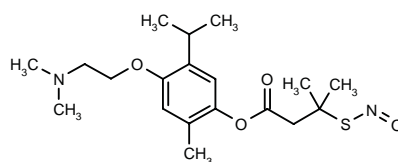
(1*R*,2*S*,4*aR*,13*bS*,14*aS*)-13-Acetyl-2-[3-methyl-3-(nitroso-sulfanyl)butanoyloxy]-1,2,3,4,4*a*,5,7,8,13,13*b*,14,14*a*-dodecahydrobenz[*g*]indolo[2,3-*a*]quinolizine-1-carboxylic acid methyl ester

S-Nitrosylated yohimbine
SNO-Yohimbine



C₂₈ H₃₅ N₃ O₆ S; Mol wt: 541.6655

ACTION – Nitrosylated α -adrenoceptor antagonist for the treatment of impotence that has both nitric oxide (NO)-donating and α -adrenoceptor-antagonist effects, a nitrosylated form of yohimbine with 10-fold selectivity for α_2 - over α_1 -adrenoceptors (K_i = 6.6 and 67 nM, respectively). In rabbit corpus cavernosum strips, compound showed α_2 -adrenoceptor-antagonist activity comparable to yohimbine, as demonstrated by pA_2 values of 8.5 and 8.9, respectively, for inhibition of UK-14304-induced contractions. It was also able to antagonize endothelin-induced contractions in human and rabbit corpus cavernosum strips and to increase cGMP levels in rabbit cavernosal tissue. *In vivo*, intracavernosal injection of compound (1 mg/kg) induced a similar but significantly longer lasting increase in intracavernosal pressure than yohimbine (1 mg/kg), with no effects on systemic mean arterial blood pressure. Another nitrosylated α -adrenoceptor antagonist (a nitrosylated form of moxisylyte) is:



NMI-221 [243598]¹⁻⁵: C₁₉ H₃₀ N₂ O₄ S

SOURCE – NitroMed.

REFERENCES

1. Carvey, D.S. et al. (NitroMed Inc.) *Nitrosated and nitrosylated α -adrenergic receptor antagonist cpds., compsns. and their uses*. WO 9727749.

2. Letts, G. *Generic enhancement through nitrosylation: The creation of new and novel NO donors using established drugs as templates*. IBC 6th Annu Conf Nitric Oxide. Nov Ther Clin Appl (May 8-9, Philadelphia) 1997, 1997.

3. Sáenz de Tejada, I. et al. *Design and evaluation of nitrosylated α -adrenergic receptor antagonists as potential agents for the treatment of impotence*. J Pharmacol Exp Ther 1999, 290(1): 121.

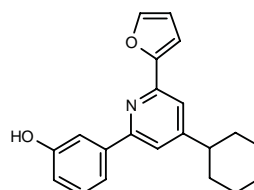
4. Saenz de Tejada, I. et al. *S-Nitrosylated α blockers as potential drugs for the treatment of impotence: Biological activity of NMI-187 and NMI-221*. Int J Impot Res 1996, 8(3): Abst A16.

5. Saenz de Tejada, I. et al. *Nitrosylated α -adrenergic receptor antagonists as potential drugs for the treatment of erectile dysfunction*. J Urol 1997, 157(4, Suppl.): Abst 791.

TREATMENT OF GYNECOLOGICAL DISORDERS

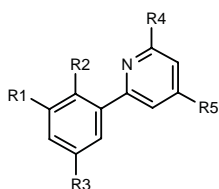
278429

3-[4-Cyclohexyl-6-(furan-2-yl)pyridin-2-yl]phenol



C₂₁ H₂₁ N O₂; Mol wt: 319.4019

ACTION – Estrogen agonist with a relative binding affinity of 36 for the estrogen receptor at 1 μ M (17 β -estradiol = 100 at 1 nM), reported to be useful in the treatment of postmenopausal disorders such as osteoporosis, atherosclerosis and Alzheimer's disease. A representative compound from a series of specifically claimed 2,4,6-trisubstituted pyridines, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
278430	H	OH	H	4-Cl-Ph	3,4-(F)2-Ph	C ₂₃ H ₁₄ ClF ₂ NO
278431	H	OH	H	2-Naph	3,4-(F)2-Ph	C ₂₇ H ₁₇ F ₂ NO
278432	H	OH	H	2-furyl	3,4-(F)2-Ph	C ₂₁ H ₁₃ F ₂ NO ₂
278433	H	OH	H	2-Naph	1,3-benzodioxol-5-yl	C ₂₈ H ₁₉ NO ₃
278434	H	OH	H	3-thienyl	1,3-benzodioxol-5-yl	C ₂₂ H ₁₅ NO ₃ S
278435	H	OH	F	2-Naph	4-Ph-Ph	C ₃₃ H ₂₂ FNO
278436	H	OH	F	4-Pyr	4-Ph-Ph	C ₂₈ H ₁₉ FN ₂ O
278437	H	OH	F	2-furyl	cyclohexyl	C ₂₁ H ₂₀ FNO ₂
278438	OH	H	H	2-Naph	4-Ph-Ph	C ₃₃ H ₂₂ FNO

SOURCE – American Home Products.

REFERENCES

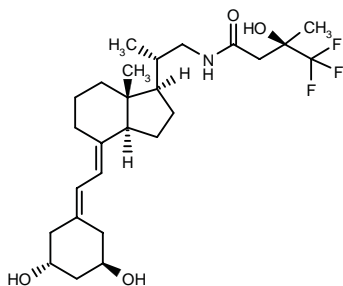
- Chiu, C. et al. (American Home Products Corp.) *2,4,6-Trisubst. pyridines with estrogenic activity and methods for the solid phase synthesis thereof*. WO 9932447.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

278021

(1*R*,3*R*,20*S*)-*N*-[1,3-Dihydroxy-20-methyl-19-nor-9,10-secopregna-5,7(*E*)-dien-21-yl]-4,4,4-trifluoro-3(*R*)-hydroxy-3-methylbutyramide



C₂₆ H₄₀ F₃ N O₄; Mol wt: 487.5990

ACTION – A representative compound from a series of vitamin D₃ amide derivatives with potential in the treatment of hyperproliferative skin diseases such as psoriasis, neoplastic diseases such as leukemia and sebaceous gland diseases such as acne. Compound exhibited comparable activity to calcitriol in a vitamin D receptor (VDR) activation assay in COS cells transfected with the human VDR (EC₅₀ = 2.1 nM vs. 2.6 nM for calcitriol), while showing much lower calcemic potential in mice, where it exhibited a highest tolerated dose (HTD) of 22 µg/kg/day s.c. for 4 days compared to 0.5 µg/kg for calcitriol. When tested in hairless mice, it promoted

epidermal thickening with an ED₅₀ of 50 µg/kg p.o. while showing an HTD of 8 µg/kg p.o., compared to ED₅₀ and HTD values for calcitriol of 500 and 1 µg/kg p.o., respectively; compound thus shows an 80-fold improved therapeutic index compared to calcitriol.

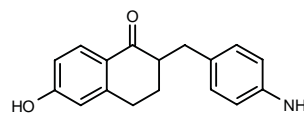
SOURCE – Roche.

REFERENCES

- Barbier, P. et al. (F. Hoffmann-La Roche AG) *Novel vitamin D₃ amide derivs.* WO 9931055.

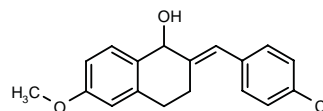
278880

2-(4-Aminobenzyl)-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenone



C₁₇ H₁₇ N O₂; Mol wt: 267.3263

ACTION – Agent for the treatment of dermatological conditions such as ichthyosis, acne, psoriasis, wrinkles or photodamaged skin that acts by inhibiting retinoic acid (RA) metabolism through inhibition of the specific P-450-RA enzyme (IC₅₀ = 1-5 µM), being more potent than ketoconazole (IC₅₀ = 18.8 µM). Preferably for topical administration. Another compound from this series of benzyl and benzyldene tetralins is:



278882: C₁₈ H₁₇ Cl O₂

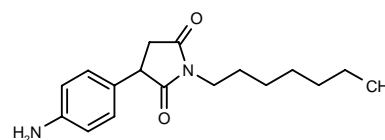
SOURCE – Cardiff University, Cardiff (GB).

REFERENCES

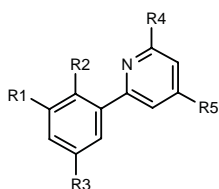
- Nicholls, P.J. et al. (Cardiff University) *Benzyl and benzyldene tetralins and derivs.* WO 9935115.

278954

3-(4-Aminophenyl)-1-heptylpyrrolidine-2,5-dione



C₁₇ H₂₄ N₂ O₂; Mol wt: 288.3886



Compound	R1	R2	R3	R4	R5	Formula
278430	H	OH	H	4-Cl-Ph	3,4-(F)2-Ph	C ₂₃ H ₁₄ ClF ₂ NO
278431	H	OH	H	2-Naph	3,4-(F)2-Ph	C ₂₇ H ₁₇ F ₂ NO
278432	H	OH	H	2-furyl	3,4-(F)2-Ph	C ₂₁ H ₁₃ F ₂ NO ₂
278433	H	OH	H	2-Naph	1,3-benzodioxol-5-yl	C ₂₈ H ₁₉ NO ₃
278434	H	OH	H	3-thienyl	1,3-benzodioxol-5-yl	C ₂₂ H ₁₅ NO ₃ S
278435	H	OH	F	2-Naph	4-Ph-Ph	C ₃₃ H ₂₂ FNO
278436	H	OH	F	4-Pyr	4-Ph-Ph	C ₂₈ H ₁₉ FN ₂ O
278437	H	OH	F	2-furyl	cyclohexyl	C ₂₁ H ₂₀ FNO ₂
278438	OH	H	H	2-Naph	4-Ph-Ph	C ₃₃ H ₂₂ FNO

SOURCE – American Home Products.

REFERENCES

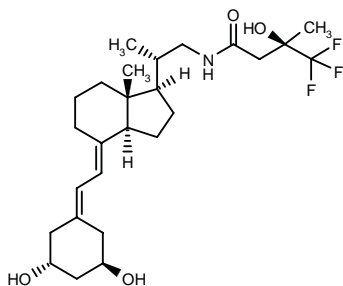
- Chiu, C. et al. (American Home Products Corp.) *2,4,6-Trisubst. pyridines with estrogenic activity and methods for the solid phase synthesis thereof*. WO 9932447.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

278021

(1*R*,3*R*,20*S*)-*N*-[1,3-Dihydroxy-20-methyl-19-nor-9,10-secopregna-5,7(*E*)-dien-21-yl]-4,4,4-trifluoro-3(*R*)-hydroxy-3-methylbutyramide



C₂₆ H₄₀ F₃ N O₄; Mol wt: 487.5990

ACTION – A representative compound from a series of vitamin D₃ amide derivatives with potential in the treatment of hyperproliferative skin diseases such as psoriasis, neoplastic diseases such as leukemia and sebaceous gland diseases such as acne. Compound exhibited comparable activity to calcitriol in a vitamin D receptor (VDR) activation assay in COS cells transfected with the human VDR (EC₅₀ = 2.1 nM vs. 2.6 nM for calcitriol), while showing much lower calcemic potential in mice, where it exhibited a highest tolerated dose (HTD) of 22 µg/kg/day s.c. for 4 days compared to 0.5 µg/kg for calcitriol. When tested in hairless mice, it promoted

epidermal thickening with an ED₅₀ of 50 µg/kg p.o. while showing an HTD of 8 µg/kg p.o., compared to ED₅₀ and HTD values for calcitriol of 500 and 1 µg/kg p.o., respectively; compound thus shows an 80-fold improved therapeutic index compared to calcitriol.

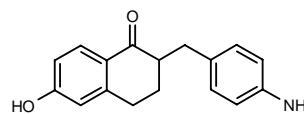
SOURCE – Roche.

REFERENCES

- Barbier, P. et al. (F. Hoffmann-La Roche AG) *Novel vitamin D₃ amide derivs.* WO 9931055.

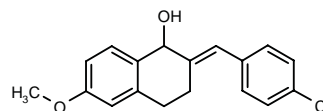
278880

2-(4-Aminobenzyl)-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenone



C₁₇ H₁₇ N O₂; Mol wt: 267.3263

ACTION – Agent for the treatment of dermatological conditions such as ichthyosis, acne, psoriasis, wrinkles or photodamaged skin that acts by inhibiting retinoic acid (RA) metabolism through inhibition of the specific P-450-RA enzyme (IC₅₀ = 1-5 µM), being more potent than ketoconazole (IC₅₀ = 18.8 µM). Preferably for topical administration. Another compound from this series of benzyl and benzyldene tetralins is:



278882: C₁₈ H₁₇ Cl O₂

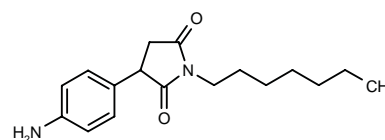
SOURCE – Cardiff University, Cardiff (GB).

REFERENCES

- Nicholls, P.J. et al. (Cardiff University) *Benzyl and benzyldene tetralins and derivs.* WO 9935115.

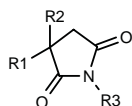
278954

3-(4-Aminophenyl)-1-heptylpyrrolidine-2,5-dione



C₁₇ H₂₄ N₂ O₂; Mol wt: 288.3886

ACTION – Agent for the treatment of dermatological conditions such as ichthyosis, acne, psoriasis, wrinkles or photodamaged skin that acts by inhibiting retinoic acid (RA) metabolism through specific inhibition of P-450-RA enzyme (80% inhibition at 100 μ M), being comparable in potency to ketoconazole (85% inhibition at 100 μ M), while showing much lower activity towards other steroidogenic P-450 enzymes such as P-450 17 α , and thus expected to exhibit less side effects. Preferably for topical administration. Other compounds from this series of succinimide derivatives include the following:



Compound	R1	R2	R3	Formula
278955	4-NH2-Ph	H	cyclohexyl	C ₁₆ H ₂₀ N ₂ O ₂
278956	4-NH2-Ph	H	C6H13	C ₁₆ H ₂₂ N ₂ O ₂
278957	4-NH2-Ph	C5H11	H	C ₁₅ H ₂₀ N ₂ O ₂
278958	4-NH2-Ph	4-NH2-Ph	C6H13	C ₂₂ H ₂₇ N ₃ O ₂
278959	4-NH2-PhCH(CH2Ph)	H	H	C ₁₈ H ₁₈ N ₂ O ₂

SOURCE – Cardiff University, Cardiff (GB).

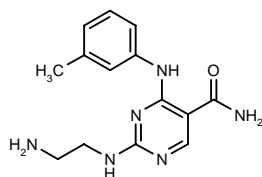
REFERENCES

1. Nicholls, P.J. et al. (Cardiff University) *Succinimide derivs. which inhibit retinoic acid metabolism*. WO 9935129.

TOPICAL ANTIALLERGIC DRUGS

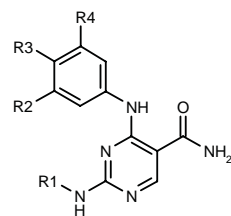
279139

2-(2-Aminoethylamino)-4-(3-methylphenylamino)pyrimidine-5-carboxamide



C₁₄ H₁₈ N₆ O; Mol wt: 286.3372

ACTION – Syk tyrosine kinase inhibitor (IC₅₀ = 0.1 μ M or less) reported to be active in a murine passive cutaneous anaphylaxis (PCA) model following s.c. administration. Other compounds from this series of pyrimidine-5-carboxamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279140	CH2CH2NH2	CF3	H	H	C ₁₄ H ₁₅ F ₃ N ₆ O
279141	(CH2)4NH2	CF3	H	H	C ₁₆ H ₁₉ F ₃ N ₆ O
279142	CH2CH2NH2	Br	H	H	C ₁₃ H ₁₅ BrN ₆ O
279143	CH2CH2NH2	NO2	H	H	C ₁₃ H ₁₅ N ₇ O ₃
279144	CH2CH2NH2	Me	H	Me	C ₁₅ H ₂₀ N ₆ O
279145	CH2CH2NH2	-CH=CHCH=CH-	H	H	C ₁₇ H ₁₈ N ₆ O
279146	cis-2-NH2-cyclohexyl	Me	H	H	C ₁₈ H ₂₄ N ₆ O
279147	cis-2-NH2-cyclohexyl	Br	H	H	C ₁₇ H ₂₁ BrN ₆ O
279148	cis-2-NH2-cyclohexyl	Cl	H	Cl	C ₁₇ H ₂₀ Cl ₂ N ₆ O
279149	cis-2-NH2-cyclohexyl	OMe	OMe	OMe	C ₂₀ H ₂₈ N ₆ O ₄

SOURCE – Yamanouchi.

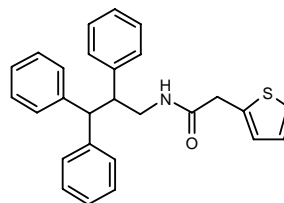
REFERENCES

1. Hisamichi, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel pyrimidine-5-carboxamide derivs.* WO 9931073.

TOPICAL ANTIINFLAMMATORY DRUGS

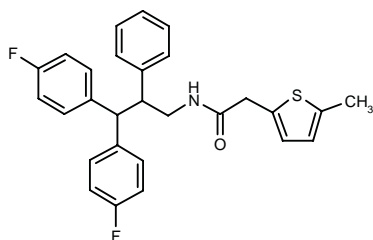
278735

2-(2-Thienyl)-N-(2,3,3-triphenylpropyl)acetamide



C₂₇ H₂₅ N O S; Mol wt: 411.5665

ACTION – Topical antiinflammatory agent with high affinity and selectivity for the human glucocorticoid receptor (hGR; IC₅₀ = 8 nM) relative to the human progesterone receptor (28.3% inhibition at 10 μ M) and which is reported to be devoid of glucocorticoid-like side effects. Compound exhibited comparable activity to hydrocortisone against oxazolone-induced contact mouse ear edema (83% inhibition at 1 mg vs. 75-85% inhibition for hydrocortisone at the same concentration) and was only slightly less active than hydrocortisone against TPA-induced mouse ear edema (64.9% inhibition vs. 80.6% inhibition for hydrocortisone, both given at 1%). Another compound from this series of triphenylpropanamide derivatives is:



278736: C₂₈ H₂₅ F₂ N O S

SOURCE – Ortho-McNeil.

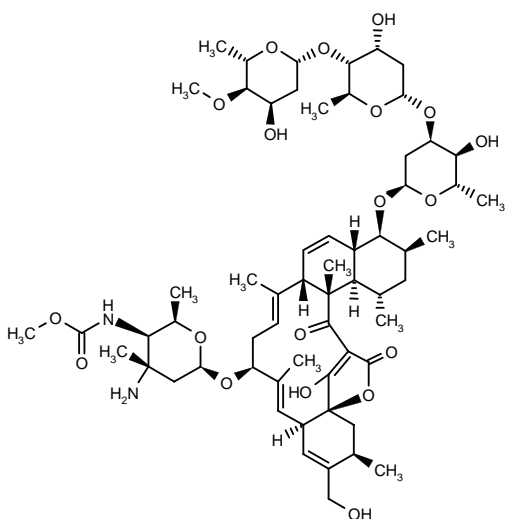
REFERENCES

1. Scott, M. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Anti-inflammatory cpds.* WO 9933786.

LOBOPHORIN A¹

278862

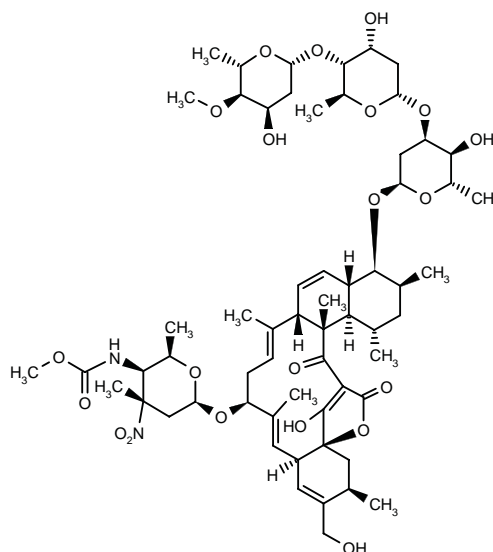
(1*S*,3*S*,4*S*,4*aS*,6*aS*,7*E*,10*S*,11*E*,12*aS*,15*R*,16*aS*,20*aS*,20*bR*)-10-[3-Amino-4-(methoxycarboxamido)-3-*C*-methyl-2,3,4,6-tetra-deoxy-β-D-idopyranosyloxy]-4-[*O*-2,6-dideoxy-4-*O*-methyl-β-L-allopyranosyl-(1→4)-*O*-2,6-dideoxy-α-L-allopyranosyl-(1→3)-*O*-2,6-dideoxy-α-L-allopyranosyloxy]-21-hydroxy-1,3,7,11,15,20a-hexamethyl-2,3,4,4a,6a,9,10,12a,15,16,20a,20b-dodecahydro-18*H*-16a,19-metheno-16a*H*-benzo[*b*]-naphth[2,1-*f*]oxacyclotetradecin-18,20(1*H*)-dione



C₆₁ H₉₂ N₂ O₁₉; Mol wt: 1157.3930

$[\alpha]_D^{22} -175^\circ$ (c 0.28, MeOH).

ACTION – Antiinflammatory agent, a macrolide produced by a tropical marine bacterium isolated from the surface of the Caribbean brown alga *Lobophora variegata*, proven to reduce PMA-induced mouse ear edema when given topically (86% reduction at 50 μg/ear). It did not show significant antibacterial activity. Another related compound is:



Lobophorin B [278863]¹⁻⁴: C₆₁ H₉₀ N₂ O₂₁

Lobophorin B, reported as a metaperiodate reaction product of kijanimicin, was also effective following i.p. administration.

SOURCE – Scripps Institution of Oceanography, La Jolla, CA (US).

REFERENCES

- Jiang, Z.-D. et al. *Lobophorins A and B, new antiinflammatory macrolides produced by a tropical marine bacterium.* Bioorg Med Chem Lett 1999, 9(14): 2003.
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- Pramanik, B.N. et al. *Special techniques of fast atom bombardment mass spectrometry for the study of oligosaccharide containing macrotetronolide antibiotic, kijanimicin.* J Antibiot 1984, 37(7): 818.

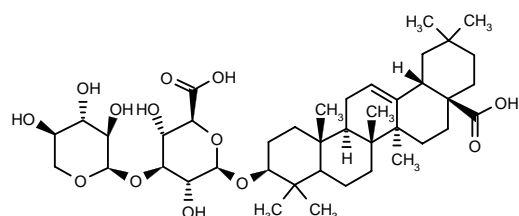
OTHER DERMATOLOGIC DRUGS

MOMORDIN Ic

252496

[4*aS*-(4*aα*,6*aβ*,6*bα*,10*α*,12*aα*,12*bβ*,14*bα*)]-2,2,6a,9,9,12a-Heptamethyl-10-[3-*O*-(α-D-xylopyranosyl)-β-D-glucopyranosyl-1-*O*-yluronic acid]-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydricene-4a-carboxylic acid

1-*O*-(17-Carboxy-28-norolean-12-en-3β-yl)-3-*O*-(β-D-xylopyranosyl)-β-D-glucopyranuronic acid



C₄₁ H₆₄ O₁₃; Mol wt: 764.9436

ACTION – Oleanolic acid oligoglycoside extracted from the traditional Chinese herb *Kochia fructus* (dried fruits of *Kochia scoparia* L.) with many pharmacological effects including antinociceptive and antiinflammatory, anti-allergic, antipruritic, hypoglycemic effects, as well as inhibitory effects on gastric emptying and gastrointestinal transit and protective effects on gastric lesions induced by indomethacin. Potentially useful for the treatment of allergic or inflammatory diseases associated with pruritogenic symptoms, for the prevention and treatment of type II diabetes and for the treatment of ileus and gastrointestinal motility disorders.

SOURCES – Dainippon Pharmaceutical; Kyoto Pharmaceutical University, Kyoto (JP).

REFERENCES

- Kubo, M. et al. (Dainippon Pharmaceutical Co., Ltd.) *Antipruritic agents of oleanolic acids*. JP 99012178.
- Matsuda, H. et al. (Dainippon Pharmaceutical Co., Ltd.) *Antipruritic agents derived from Kochia scoparia* (L.). JP 98245395.
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- Matsuda, H. et al. *Studies on Kochia fructus IV. Anti-allergic of 70% ethanol extract and its component, momordin Ic from dried fruits of Kochia scoparia L.* Biol Pharm Bull 1997, 20(11): 1165.
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- Yoshikawa, M. et al. *Medical foodstuffs. VII. On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish "Tonburi", the fruit of Japanese Kochia scoparia (L.) SCHRAD.: Structures of scopariosides A, B, and C*. Chem Pharm Bull 1997, 45(8): 1300.
- Yoshikawa, M. et al. *Studies on Kochia Fructus. II. On the saponin constituents from the fruit of Chinese Kochia scoparia (Chenopodiaceae): Chemical structures of kochianosides I, II, III, and IV*. Chem Pharm Bull 1997, 45(6): 1055.

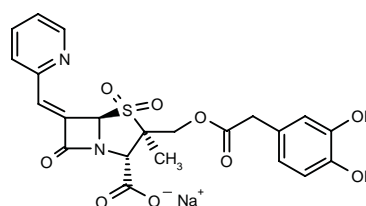
ANTIINFECTIVE THERAPY

ANTIBIOTICS

274226

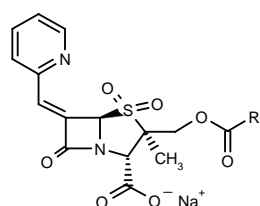
2-(3,4-Dihydroxyphenyl)acetic acid (2*R*,3*S*,5*R*)-3-carboxy-2-methyl-1,1-dioxo-6-[(*E*)-pyridin-2-ylmethylene]-penam-2-ylmethyl ester sodium salt

(2*S*,3*R*,5*R*)-3-[2-(3,4-Dihydroxyphenyl)acetoxymethyl]-3-methyl-4,4,7-trioxo-6-[(*Z*)-2-pyridinylmethylene]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid sodium salt



C22 H19 N2 Na O9 S; Mol wt: 510.4531

ACTION – Penam-derived inhibitor of both class A and class C β -lactamases with high synergistic activity when given with antibacterial compounds, especially against Gram-negative bacterial strains. When administered simultaneously with piperacillin, it dramatically improved the antibacterial effect of the latter, in particular against *Pseudomonas aeruginosa* GC 1764, *Aeromonas sobria* GC 2069 and *Serratia marcescens* GC 4132, reducing the MICs from 64 μ g/ml or more to 1-4 μ g/ml; it was more active than tazobactam, which reduced MICs only to 16-64 μ g/ml.



Compound	R1	Formula
274223	Me	C ₁₆ H ₁₅ N ₂ NaO ₇ S
274225	CH ₂ Ph	C ₂₂ H ₁₉ N ₂ NaO ₇ S

SOURCE – Research Corporation Technologies.

REFERENCES

- Buynak, J.D. and Rao, A.S. (Research Corporation Technologies, Inc.) *2- β -Substd.-6-alkylidene penicillanic acid derivs. as β -lactamase inhibitors*. WO 9933838.
- Buynak, J.D. et al. *New beta-lactamase inhibitors of the class A and class C enzymes*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI-194.

ACTION – Oleanolic acid oligoglycoside extracted from the traditional Chinese herb *Kochia fructus* (dried fruits of *Kochia scoparia* L.) with many pharmacological effects including antinociceptive and antiinflammatory, anti-allergic, antipruritic, hypoglycemic effects, as well as inhibitory effects on gastric emptying and gastrointestinal transit and protective effects on gastric lesions induced by indomethacin. Potentially useful for the treatment of allergic or inflammatory diseases associated with pruritogenic symptoms, for the prevention and treatment of type II diabetes and for the treatment of ileus and gastrointestinal motility disorders.

SOURCES – Dainippon Pharmaceutical; Kyoto Pharmaceutical University, Kyoto (JP).

REFERENCES

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- Matsuda, H. et al. *Inhibitory mechanism of oleanolic acid 3-O-monodesmosides on glucose absorption in rats*. Biol Pharm Bull 1997, 20(6): 717.
- Matsuda, H. et al. *Protective effects of oleanolic acid oligoglycosides on ethanol- or indomethacin-induced gastric mucosal lesions in rats*. Life Sci 1998, 63(17): PL245.
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- Matsuda, H. et al. *Studies on Kochia fructus IV. Anti-allergic of 70% ethanol extract and its component, momordin Ic from dried fruits of Kochia scoparia L.* Biol Pharm Bull 1997, 20(11): 1165.
- Matsuda, H. et al. *Studies on Kochia Fructus. V. Antipruritic effects of oleanolic acid glycosides and the structure-requirement*. Biol Pharm Bull 1998, 21(11): 1231.
- Odukoya, O.A. et al. *Molluscicidal triterpenoid glycosides of Dalium guineense*. J Nat Prod 1996, 59(6): 632.
- Wen, Y. et al. *Chemical constituents of fruit of belvedere (Kochia scoparia)*. Zhongcaoyao 1993, 24(1): 5.
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- Yoshikawa, M. et al. *Studies on Kochia Fructus. II. On the saponin constituents from the fruit of Chinese Kochia scoparia (Chenopodiaceae): Chemical structures of kochianosides I, II, III, and IV*. Chem Pharm Bull 1997, 45(6): 1055.

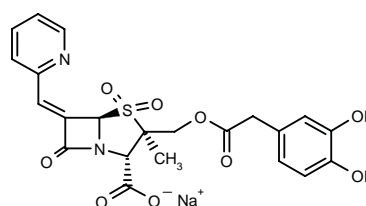
ANTIINFECTIVE THERAPY

ANTIBIOTICS

274226

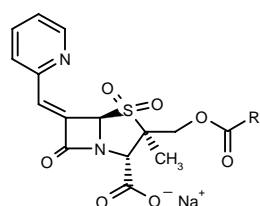
2-(3,4-Dihydroxyphenyl)acetic acid (2*R*,3*S*,5*R*)-3-carboxy-2-methyl-1,1-dioxo-6-[(*E*)-pyridin-2-ylmethylene]-penam-2-ylmethyl ester sodium salt

(2*S*,3*R*,5*R*)-3-[2-(3,4-Dihydroxyphenyl)acetoxymethyl]-3-methyl-4,4,7-trioxo-6-[(*Z*)-2-pyridinylmethylene]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid sodium salt



C22 H19 N2 Na O9 S; Mol wt: 510.4531

ACTION – Penam-derived inhibitor of both class A and class C β -lactamases with high synergistic activity when given with antibacterial compounds, especially against Gram-negative bacterial strains. When administered simultaneously with piperacillin, it dramatically improved the antibacterial effect of the latter, in particular against *Pseudomonas aeruginosa* GC 1764, *Aeromonas sobria* GC 2069 and *Serratia marcescens* GC 4132, reducing the MICs from 64 μ g/ml or more to 1-4 μ g/ml; it was more active than tazobactam, which reduced MICs only to 16-64 μ g/ml.



Compound	R1	Formula
274223	Me	C ₁₆ H ₁₅ N ₂ NaO ₇ S
274225	CH ₂ Ph	C ₂₂ H ₁₉ N ₂ NaO ₇ S

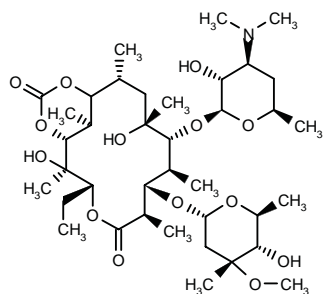
SOURCE – Research Corporation Technologies.

REFERENCES

- Buynak, J.D. and Rao, A.S. (Research Corporation Technologies, Inc.) *2- β -Substd.-6-alkylidene penicillanic acid derivs. as β -lactamase inhibitors*. WO 9933838.
- Buynak, J.D. et al. *New beta-lactamase inhibitors of the class A and class C enzymes*. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI-194.

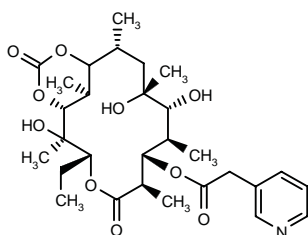
277499

9-Deoxy-9-hydroxyerythromycin A 9-*O*,11-*O*-cyclic carbonate

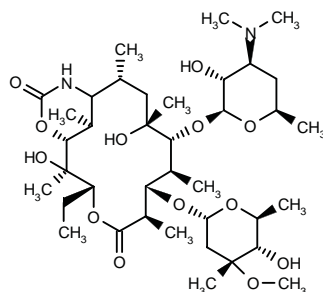


C38 H67 N O14; Mol wt: 761.9403

ACTION – Macrolide antibiotic, a representative compound from a series of erythromycin A derivatives, wherein the following are also included:



277500: C29 H43 N O10



277501: C38 H68 N2 O13

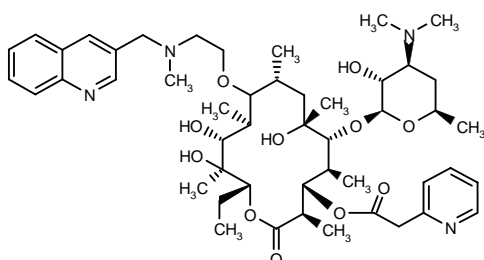
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 9921867.

277502

9-Deoxy-3-*O*-des(hexopyranosyl)-9-*O*-[2-*N*-methyl-*N*-(3-quinolylmethyl)amino]ethoxy]-3-*O*-[2-(2-pyridyl)acetyl]-erythromycin A



C49 H74 N4 O11; Mol wt: 895.1406

ACTION – Erythromycin A-derived antibiotic with activity against a range of Gram-positive bacteria including *Staphylococcus aureus* strains, *Staphylococcus epidermidis* and *Enterococcus faecalis*, showing MICs of 1.56-6.25 µg/ml against these pathogens.

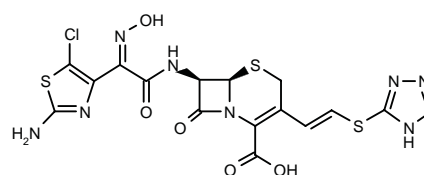
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 9921868.

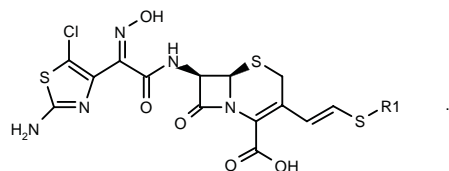
277581

(6*R*,7*R*)-7-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[2-(4*H*-1,2,4-triazol-3-ylsulfanyl)vinyl]-3-cephem-4-carboxylic acid

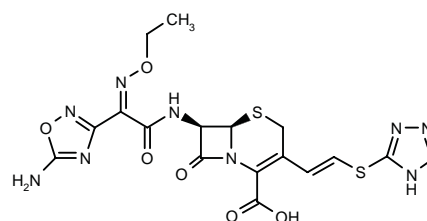


C16 H13 Cl N8 O5 S3; Mol wt: 528.9807

ACTION – A representative compound from a series of cephem antibiotics wherein the following are also included:



Compound	R1	X	Formula
277583	2(S)-pyrrolidinyl-CH2		C ₁₉ H ₂₁ ClN ₈ O ₅ S ₃
277584	1-[MeC(=NH)]-2(S)-pyrrolidinyl-CH2		C ₂₁ H ₂₄ ClN ₇ O ₅ S ₃
277585	1-Piz-CH2CH2	HCl	C ₂₀ H ₂₄ ClN ₇ O ₅ S ₃ ·HCl



277582: C17 H17 N9 O6 S2

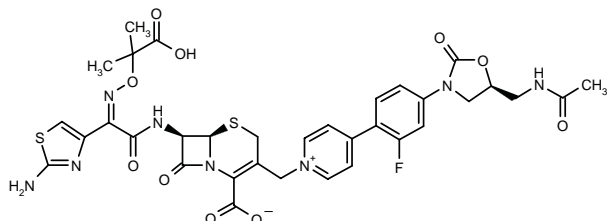
SOURCE – Fujisawa.

REFERENCES

1. Kawabata, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel cephem cpds.* WO 9919330.

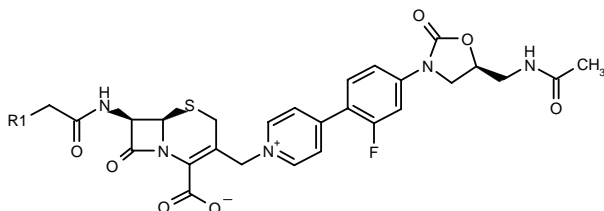
278621

(6*R*,7*R*)-3-[4-[4-[5(*S*)-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl]pyridinium-1-ylmethyl]-7-[2-(2-aminothiazol-4-yl)-2(*Z*)-(1-carboxy-1-methylethoxyimino)-acetamido]-3-cephem-4-carboxylate



C34 H33 F N8 O10 S2; Mol wt: 796.8107

ACTION – Antibacterial agent with good aqueous solubility and a broad spectrum of activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* C5100 (MIC = 2.00 µg/ml vs. 32 and 1.00 µg/ml for cefotaxime and vancomycin, respectively), ciprofloxacin-resistant *S. aureus* C6043 (MIC = 2.00 µg/ml vs. 128 and 1.00 µg/ml for cefotaxime and vancomycin, respectively), *Enterococcus faecalis* ATCC29212 (MIC = 2.00 µg/ml vs. 128 and 2.00 µg/ml for cefotaxime and vancomycin, respectively), *Escherichia coli* ATCC10536 (MIC = 0.25 µg/ml vs. 0.06 and 128 µg/ml for cefotaxime and vancomycin, respectively) and *Klebsiella pneumoniae* ATCC10031 (MIC = 0.12 µg/ml vs. 0.06 and 128 µg/ml for cefotaxime and vancomycin, respectively). LD₅₀ = 1500 mg/kg i.v. in mice. Other compounds within this series of antibacterial agents combining an oxazolidinone moiety with a cephem include the following:



Compound	R1	Formula
278622	H	C ₂₇ H ₂₆ FN ₅ O ₇ S
278623	OH	C ₂₇ H ₂₆ FN ₅ O ₈ S

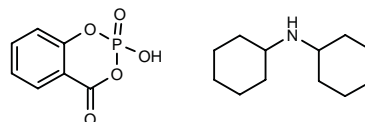
SOURCE – Cheil Jedang.

REFERENCES

1. Yoon, Y.H. et al. (Cheil Jedang Corporation) *Cephem derivs. and methods for producing the cpds. and an antibacterial compsn. containing the cpds.* WO 9933839.

278699

2-Hydroxy-4*H*-1,3,2λ⁵-benzodioxaphosphorin-2,4-dione dicyclohexylamine salt



C12 H23 N . C7 H5 O5 P; Mol wt: 381.4062

ACTION – β-Lactamase inhibitor that is able to enhance the activity of β-lactam antibiotics in the treatment of bacterial infections, being more potent than clavulanic acid against *Enterobacter cloacae* P99 β-lactamase. In addition, it exhibits antibacterial activity through inhibition of bacterial DD-peptidases and was shown to produce a 2-fold increase in the activity of piperacillin against *Staphylococcus aureus* ATCC29213 at a concentration of 100 µg/ml.

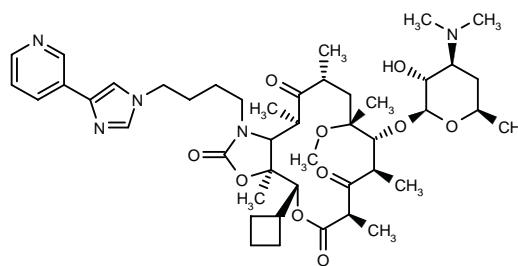
SOURCES – MethylGene; Wesleyan University, Middletown, CT (US).

REFERENCES

1. Besterman, J.M. et al. (MethylGene Inc.; Wesleyan University) *Novel β-lactamase and DD-peptidase inhibitors.* WO 9933850.

278852

13-Cyclobutyl-11-deoxy-13-desethyl-3-des(hexo-pyranosyloxy)-6-*O*-methyl-3-oxo-11-[4-[4-(3-pyridinyl)-1*H*-imidazol-1-yl]butylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C45 H67 N5 O10; Mol wt: 838.0493

ACTION – Erythromycin derivative with potential in the treatment of bacterial and protozoal infections.

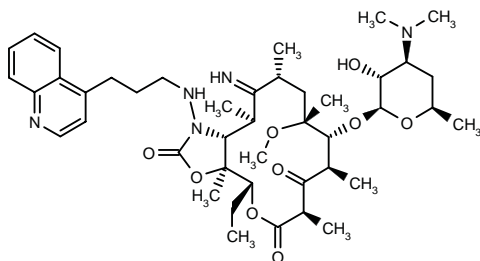
SOURCE – Pfizer.

REFERENCES

1. Wu, Y.-J. (Pfizer Products Inc.) *Novel erythromycin derivs.* WO 9935157.

278895

3-Des(hexopyranosyloxy)-9-deoxo-11-deoxy-9-imino-6-O-methyl-3-oxo-11-[3-(quinolin-4-yl)propylhydrazino]-erythromycin A 11-N¹,12-O-cyclic carbamate



C43 H65 N5 O9; Mol wt: 796.0125

ACTION – A representative compound from a series of 9-amino-3-keto-erythromycin derivatives with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, as well as protozoa.

SOURCE – Pfizer.

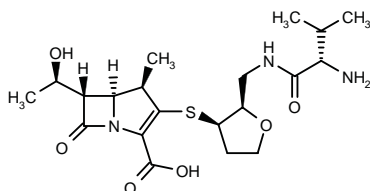
REFERENCES

1. Wu, Y.-J. (Pfizer Products Inc.) *9-Amino-3-keto erythromycin derivs.* WO 9921866.

OCA-983*

255606

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[2(*R*)-(L-valylaminomethyl)tetrahydrofuran-3(*R*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C20 H30 N2 O7 S; Mol wt: 442.5300

ACTION – Carbapenem antibiotic, a peptidic, orally active prodrug of the THF 1-β-methylcarbapenem CL-191121⁺, proven active *in vitro* against *Staphylococcus aureus* and *Escherichia coli* (MIC = 0.25 and 0.06 μg/ml or less, respectively) as well as against lethal infections caused by *S. aureus* and *E. coli* in mice (ED₅₀ = 0.1 and 0.31 mg/kg p.o., respectively; 0.07 and 0.29 mg/kg s.c., respectively), with significantly improved oral activity compared to the parent compound.

SOURCE – Wyeth-Ayerst.

REFERENCES

1. Lin, Y.-I. et al. (American Cyanamid Co.) *Novel 2-thiosubst. carbapenems.* CA 2118961, EP 617036, JP 93321948, US 56021118.

2. Bitha, P. et al. *Convergent synthesis of oral 1β-methylcarbapenems.* J Antibiot 1999, 52(7): 643.

3. Lin, Y.-I. et al. *Peptidic prodrugs of novel aminomethyl-THF 1β-methylcarbapenems.* Bioorg Med Chem Lett 1997, 7(13): 1665.

4. Weiss, W.J. et al. *In vivo activity of peptidic prodrugs of novel aminomethyl THF 1β-methylcarbapenems.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-221.

5. Weiss, W.J. et al. *In vivo activities of peptidic prodrugs of novel aminomethyl tetrahydrofuran-1β-methylcarbapenems.* Antimicrob Agents Chemother 1999, 43(3): 460.

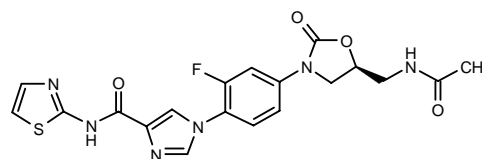
*Identified compound **255606** Drug Data Rep 1997, 019(11): 1008.

*Drug Data Rep 1995, 017(01): 0065.

ANTIBACTERIAL DRUGS

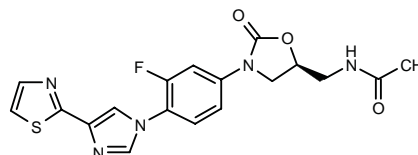
277541

1-[4-[5(*S*)-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl]-*N*-(2-thiazolyl)-1*H*-imidazole-4-carboxamide



C19 H17 F N6 O4 S; Mol wt: 444.4453

ACTION – Oxazolidinone antibacterial agent active against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS), and in particular against strains exhibiting resistance to vancomycin and against *Enterococcus faecium* resistant to both aminoglycosides and β-lactams. It showed MIC values of 0.125, 0.06, 0.125, 0.5 and 0.25 μg/ml against *Staphylococcus aureus* Oxford, coagulase-negative staphylococci, *Streptococcus pyogenes* C203, *Enterococcus faecalis* and *Bacillus subtilis*, respectively. Another specifically claimed substituted phenyloxazolidinone is:



277542: C18 H16 F N5 O3 S

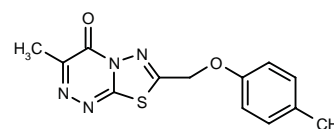
SOURCE – AstraZeneca.

REFERENCES

1. Betts, M.J. and Swain, M.L. (Zeneca Ltd.) *Subst. phenyloxazolidinones and their use as antibiotics.* WO 9928317.

278678

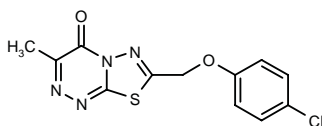
3-Methyl-7-(4-methylphenoxy)methyl)-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one



C13 H12 N4 O2 S; Mol wt: 288.3298

M.p. 205 °C.

ACTION – Antibacterial agent with broad-spectrum activity including *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* (MIC = 6-12.5 μg/ml). Another thiadiazolotriazinone with antibacterial activity is:



278679: C₁₂ H₉ Cl N₄ O₂ S

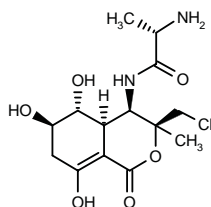
SOURCES – Kasturba Medical College, Mangalore (IN); Mangalore University, Mangalore (IN).

REFERENCES

1. Holla, B.S. et al. *Synthesis of some new biologically active thiazolotriazinones - Part II.* *Farmaco* 1999, 54(3): 149.

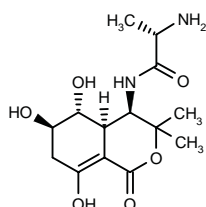
278923

2(*S*)-Amino-*N*-[3(*S*)-(chloromethyl)-5(*R*),6(*R*),8-trihydroxy-3-methyl-1-oxo-3,4,4a(*R*),5,6,7-hexahydro-1*H*-2-benzopyran-4(*R*)-yl]propionamide



C₁₄ H₂₁ Cl N₂ O₆; Mol wt: 348.7809

ACTION – Antibacterial agent active *in vitro* against Gram-positive and Gram-negative bacteria such as methicillin-resistant *Staphylococcus aureus* No. 17 (MIC = 0.78 µg/ml), *Micrococcus luteus* PCI 1001 (MIC = 0.20 µg/ml) and *Escherichia coli* NIHJ (MIC = 0.78 µg/ml). LD₅₀ > 25 mg/kg i.v. in mice. Another compound from this series of bactobolin derivatives is:



278924: C₁₄ H₂₂ N₂ O₆

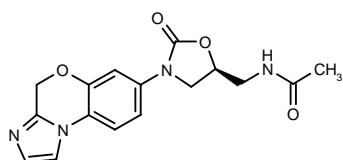
SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

1. Nishimura, Y. et al. (Microbial Chemistry Research Foundation) *Novel antibacterial bactoboline derivs., and their preparation method.* JP 99140074.

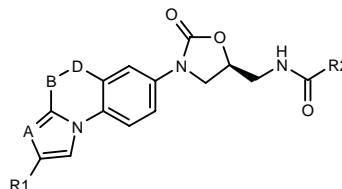
279884

N-[3-(4*H*-Imidazo[2,1-*c*][1,4]benzoxazin-7-yl)-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide

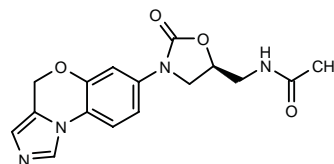


C₁₆ H₁₆ N₄ O₄; Mol wt: 328.3264

ACTION – Oxazolidinone antibacterial agent with low toxicity and a broad spectrum of activity including Gram-positive and some Gram-negative bacteria; it is reported to have good activity against *Staphylococcus aureus* 133 and *Mycobacterium smegmatis* DSM 43465. Other exemplified oxazolidinones with azole-containing tricycles are:



Compound	R1	R2	A	B	D	Formula
279885	Me	Me	N	CH ₂	O	C ₁₇ H ₁₈ N ₄ O ₄
279886	H	Et	N	CH ₂	O	C ₁₇ H ₁₈ N ₄ O ₄
279887	H	OMe	N	CH ₂	O	C ₁₆ H ₁₆ N ₄ O ₅
279888	H	Me	CH	CH ₂	O	C ₁₇ H ₁₇ N ₃ O ₄
279889	H	Me	N	CH ₂	S	C ₁₆ H ₁₆ N ₄ O ₃ S
279890	H	Me	N	S	CH ₂	C ₁₆ H ₁₆ N ₄ O ₃ S



279891: C₁₆ H₁₆ N₄ O₄

SOURCE – Bayer.

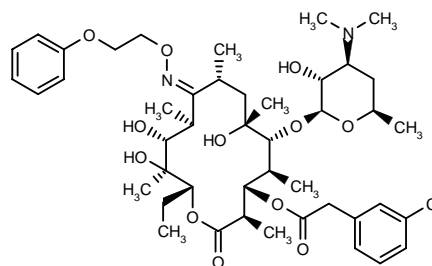
REFERENCES

1. Raddatz, S. et al. (Bayer AG) *New oxazolidinones with azol-containing tricycles.* DE 19805117, WO 9940094.

ANTIMYCOBACTERIAL AGENTS

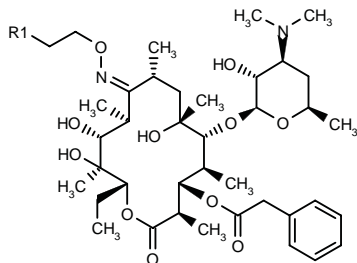
278561

3-*O*-[2-(3-Chlorophenyl)acetyl]-3-des(hexopyranosyl)-erythromycin A 9-[*O*-(2-phenoxyethyl)oxime]



C₄₅ H₆₇ Cl N₂ O₁₂; Mol wt: 863.4793

ACTION – Antibacterial agent with activity against acid-fast bacteria such as *Mycobacterium avium* 20096 (MIC = 1.56 µg/ml vs. > 50 and 3.13 µg/ml, respectively, for clarithromycin and rifampicin) and *Mycobacterium intracellulare* 20066 (MIC = 0.78 µg/ml vs. 3.13 and 3.13 µg/ml, respectively, for clarithromycin and rifampicin). Within this series of erythromycin derivatives, the following compounds are also included:



Compound	R1	Formula
278562	Ph	C ₄₆ H ₇₀ N ₂ O ₁₁
278563	CH ₂ Ph	C ₄₆ H ₇₀ N ₂ O ₁₁

SOURCE – Hokuriku.

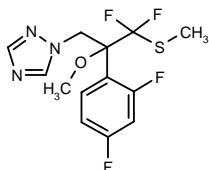
REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Erythromycin derivs.* JP 99236395, WO 9929709.

ANTIFUNGAL AGENTS

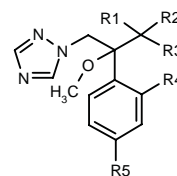
277592

1-[2-(2,4-Difluorophenyl)-3,3-difluoro-2-methoxy-3-(methylsulfanyl)propyl]-1*H*-1,2,4-triazole



C₁₃ H₁₃ F₄ N₃ O S; Mol wt: 335.3237

ACTION – Antifungal agent proven to be more active than fluconazole *in vitro* against *Candida albicans*, *Aspergillus fumigatus* and *Aspergillus flavus* strains. It also significantly increased survival compared to control and fluconazole-treated mice infected with *C. albicans* following oral administration at a dose of 1.25 mg/kg x 4. Other exemplified triazoles include the following:



Compound	R1=R2	R3	R4	R5	Formula
277593	F	SCH ₂ CH ₂ OMe	F	F	C ₁₅ H ₁₇ F ₄ N ₃ O ₂ S
277594	F	SO ₂ CH ₂ CH ₂ OMe	F	F	C ₁₅ H ₁₇ F ₄ N ₃ O ₄ S
277595	F	SO ₂ CH ₂ CH ₂ OH	F	F	C ₁₄ H ₁₅ F ₄ N ₃ O ₄ S
277596	Me	SMe	H	CF ₃	C ₁₆ H ₂₀ F ₄ N ₃ O ₃ S
277597	F	SO ₂ Me	F	F	C ₁₃ H ₁₃ F ₄ N ₃ O ₃ S

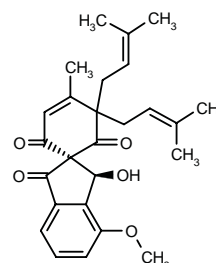
SOURCE – SSP.

REFERENCES

1. Kaneko, Y. et al. (SSP Co., Ltd.) *Triazole derivs. or their salts.* CA 2246125, JP 99130758.

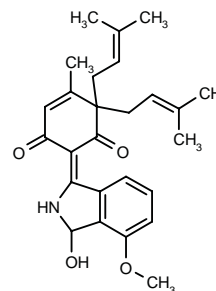
278486

(1*S*,3'*S*)-3'-Hydroxy-4'-methoxy-4-methyl-5,5-bis(3-methyl-2-butenyl)spiro[3-cyclohexene-1,2'-[2*H*]indene]-1',2,6(3'*H*)-trione



C₂₆ H₃₀ O₅; Mol wt: 422.5180

ACTION – Antifungal agent isolated from *Stachybotrys parvispora* Hughes 1952 RF-10131 (FERM P-16449) that acts as a chymase inhibitor. Another 2*H*-indene-spiro-(3'-cyclohexene) compound isolated from the same source is:



278487: C₂₆ H₃₁ N O₄

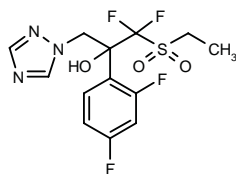
SOURCE – Shionogi.

REFERENCES

1. Kamigakiuchi, T. et al. (Shionogi & Co. Ltd.) *2H-Indene-spiro-(3'-cyclohexene) cpds.* JP 99158109.

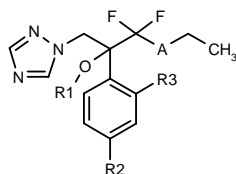
278835

2-(2,4-Difluorophenyl)-1-(ethylsulfonyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol



C13 H13 F4 N3 O3 S; Mol wt: 367.3217

ACTION – Orally active triazole antifungal agent with potent activity against *Candida albicans* ATCC 44859 (terminal point = 31.3 ng/ml) and *Aspergillus fumigatus* IFM 40808 (MIC = 8 µg/ml), being more potent than fluconazole (terminal point = 250 ng/ml and MIC > 128 µg/ml, respectively). *In vivo* activity was demonstrated in a murine model of systemic candidosis, where 4 of 5 animals survived to day 14 after infection at a dose of 1.25 mg/kg p.o. given at 1 and 24 h postinfection followed by daily treatment for the next 4 days, compared to only 1 of 5 animals treated with fluconazole at the same dose. Other compounds from this series of triazole derivatives include the following:



Compound	R1	R2	R3	A	Isomer	Formula
278836	H	F	F	S		C ₁₃ H ₁₃ F ₄ N ₃ OS
278837	H	F	H	S		C ₁₃ H ₁₄ F ₃ N ₃ OS
278838	H	CF ₃	H	S		C ₁₄ H ₁₄ F ₅ N ₃ OS
278839	H	Cl	Cl	S		C ₁₃ H ₁₃ Cl ₂ F ₂ N ₃ OS
278840	Me	F	F	S		C ₁₄ H ₁₅ F ₄ N ₃ OS
278841	H	Cl	H	SO ₂		C ₁₃ H ₁₃ Cl ₂ F ₂ N ₃ O ₃ S
278842	H	F	F	SO ₂	(-)	C ₁₃ H ₁₃ F ₄ N ₃ O ₃ S
278843	H	F	H	SO ₂	(-)	C ₁₃ H ₁₄ F ₃ N ₃ O ₃ S

SOURCE – SSP.

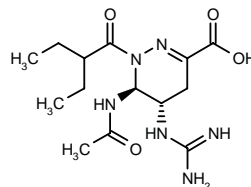
REFERENCES

1. Takeda, S. et al. (SSP Co., Ltd.) Triazole deriv. or salt thereof, preparation process thereof as well as pharmaceutical containing said cpd. CA 2256060, EP 927719.

ANTIVIRAL DRUGS

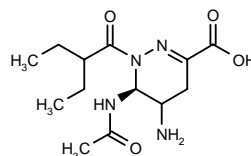
274052

trans-6-Acetamido-5-guanidino-1-(2-ethylbutanoyl)-1,4,5,6-tetrahydropyridazine-3-carboxylic acid



C14 H24 N6 O4; Mol wt: 340.3816

ACTION – Antiviral agent for the treatment of influenza infection, a potent inhibitor of neuraminidase with > 100-fold selectivity for influenza A over influenza B enzyme (IC₅₀ = 0.14 and 22 µM, respectively). Within this series of 1,4,5,6-tetrahydropyridazine derivatives, the following are also included:



Compound	Isomer	Formula
274050	trans	C ₁₃ H ₂₂ N ₄ O ₄
274053	cis	C ₁₃ H ₂₂ N ₄ O ₄

SOURCES – Gilead; Roche.

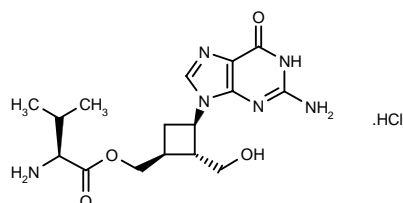
REFERENCES

1. Zhang, L. et al. Synthesis and evaluation of tetrahydropyridazine derivatives as influenza neuraminidase inhibitors. 217th ACS Natl Meet (March 21-25, Anaheim) 1999, Abst MEDI-183.
2. Zhang, L. et al. Synthesis and evaluation of 1,4,5,6-tetrahydropyridazine derivatives as influenza neuraminidase inhibitors. Bioorg Med Chem Lett 1999, 9(13): 1751.

278564

(1*R*,2*R*,3*S*)-9-[2-(Hydroxymethyl)-3-(*L*-valyloxymethyl)-cyclobutyl]guanine hydrochloride

L-Valine [(1*S*,2*R*,3*R*)-3-(2-amino-6-oxo-6,9-dihydro-1*H*-purin-9-yl)-2-(hydroxymethyl)cyclobutyl]methyl ester hydrochloride



C16 H24 N6 O4 . HCl ; Mol wt: 400.8645

ACTION – Antiviral agent, a prodrug of lobucavir* with an improved oral pharmacokinetic profile, affording higher C_{max} and AUC values for lobucavir than after administration of the parent drug in dogs.

Lobucavir is reported to be active against human cytomegalovirus, herpes simplex virus types 1 and 2, varicella-zoster virus and hepatitis B virus.

SOURCE – Bristol-Myers Squibb.

REFERENCES

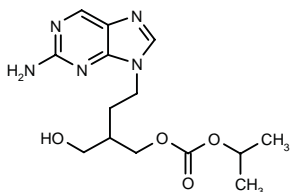
1. Zahler, R. and Murugesan, N. (Bristol-Myers Squibb Co.) *Prodrugs of lobucavir and methods of use*. WO 9932490.

*See **SQ-34514** Drug Data Rep 1991, 013(01): 0070.

SK-1875

268110

9-[3-(Hydroxymethyl)-4-(isopropoxycarbonyloxy)butyl]-purine-2-amine



C14 H21 N5 O4; Mol wt: 323.3509

ACTION – A potential prodrug of the antiviral agent penciclovir* providing high mean urinary recovery of penciclovir (53%) following oral administration in mice, as well as high stability at pH 1.2, 6.0, 7.4 and 8.0, and high water solubility (138.8 mg/ml).

SOURCE – SK Chemicals.

REFERENCES

1. Kim, D.-K. et al. *Synthesis and evaluation of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as potential prodrugs of penciclovir*. J Med Chem 1998, 41(18): 3435.

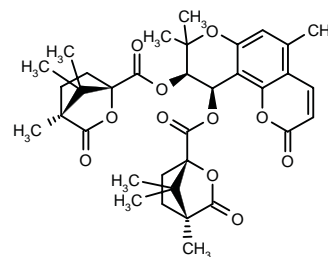
2. Kim, D.K. et al. *Synthesis of carbon-14 labelled 2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK 1875), a potential prodrug of penciclovir*. J Label Compd Radiopharm 1999, 42(6): 597.

*Drug Data Rep 1996, 018(06): 0548.

AIDS MEDICINES

278674^{1,2}

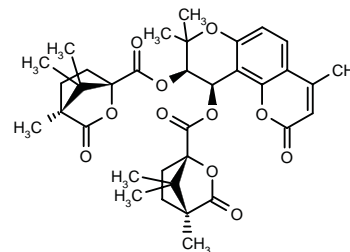
(1*S*,1'*S*,4*R*,4'*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylic acid (9*R*,10*R*)-5,8,8-trimethyl-2-oxo-9,10-dihydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-9,10-diyl ester



C35 H40 O11; Mol wt: 636.6900

White solid, *m.p.* 163-4 °C; $[\alpha]_D^{20} +18.92^\circ$ (*c* 0.37, CHCl₃).

ACTION – Anti-HIV agent with potent inhibitory activity against HIV-1 replication in both H9 lymphocytes and CEM-SS cells (EC_{50} = 0.239 and 0.0635 μ M, respectively) and low cytotoxicity (IC_{50} > 95 μ M); compound was more potent and selective than zidovudine (AZT) or the parent compound DCK. Another related compound is:



278673²: C35 H40 O11

SOURCE – Biotech Research Laboratories.

REFERENCES

1. Xie, L. et al. *Anti-AIDS agent 33. Synthesis and anti-HIV activity of mono-methyl substituted 3',4'-di-O-(–)-camphanoyl-(+)-cis-khellactone (DCK) analogues*. Bioorg Med Chem Lett 1998, 8(16): 2151.

2. Xie, L. et al. *Anti-AIDS agents. 37.(1) Synthesis and structure-activity relationships of (3'R,4'R)-(+)-cis-khellactone derivatives as novel potent anti-HIV agents*. J Med Chem 1999, 42(14): 2662.

279825

Live vaccine for HIV

ACTION – Live vaccine for HIV using an attenuated strain of *Salmonella* engineered to express specific HIV proteins. Constructs of two recombinant plasmids containing Lpp-OmpA (*Escherichia coli* lipoprotein signal sequence linked to a portion of the *Escherichia coli* outer membrane protein OmpA) genes required for surface exposure and the gene for HIV-1 reverse transcriptase or HIV-1 Tat are inserted into an attenuated strain of *Salmonella typhimurium* SL 3261. This live vaccine was used to orally inoculate mice and was found to produce a helper T-cell response specific for the HIV antigens and antigen-specific IgA responses.

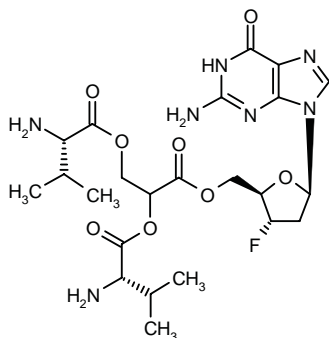
SOURCE – Research Development Foundation.

REFERENCES

1. Burnett, M.S. and Kitto, G.B. (Research Development Foundation) *Live vaccine for human immunodeficiency virus*. WO 9939735.

279938

2',3'-Dideoxy-3'-fluoro-5'-O-[2,3-bis-(L-valyloxy)propionyl]-guanosine



C23 H34 F N7 O8; Mol wt: 555.5606

ACTION – Nucleoside prodrug useful against hepatitis B virus (HBV) and HIV infections. It has good oral bioavailability, releases active drug into the blood in a relatively sustained manner and produces metabolic byproducts which are identical to compounds produced by the body. Compound provided an absolute bioavailability of the active metabolite 2',3'-dideoxy-3'-fluoroguanosine* of 64-72% over 6 h in rats.

SOURCE – Medivir.

REFERENCES

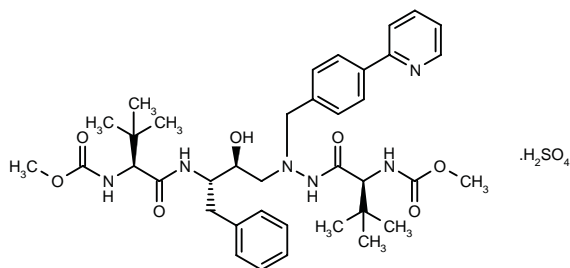
1. Wähling, H. and Zhou, X.-X. (Medivir AB) *Nucleosides*. WO 9941268.

*See **FddGuo** Drug Data Rep 1989, 011(08): 0675.

BMS-232632 BISULFATE

278962

N'-[2(*S*)-Hydroxy-3(*S*)-[*N*-(methoxycarbonyl)-*L*-*tert*-leucylamino]-4-phenylbutyl]-*N'*-(methoxycarbonyl)-*N'*-[4-(2-pyridyl)benzyl]-*L*-*tert*-leucylhydrazide sulfate



C38 H52 N6 O7 . H2 O4 S; Mol wt: 802.9416

ACTION – Bisulfate salt of the known HIV protease inhibitor BMS-232632 with superior aqueous solubility/dissolution rate and crystallinity and stability compared to other salts, and with significantly improved oral bioavailability compared to the free base.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Singh, J. et al. (Bristol-Myers Squibb Co.) *Bisulfate salt of HIV protease inhibitor*. WO 9936404.

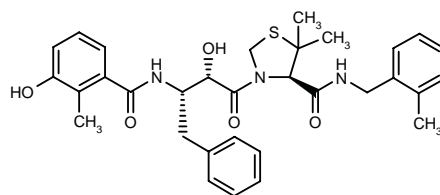
JE-2147¹⁻¹¹

264768

3-[2(*S*)-Hydroxy-3(*S*)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl]-5,5-dimethyl-*N*-(2-methylbenzyl)-thiazolidine-4(*R*)-carboxamide

AG-1776

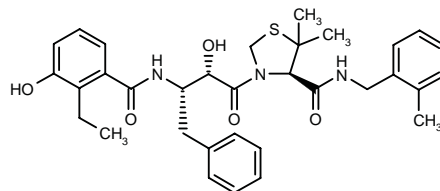
KNI-764



C32 H37 N3 O5 S; Mol wt: 575.7263

M.p. 137-9 °C.

ACTION – Orally bioavailable antiviral agent for AIDS, an allophenylnorstatine-containing dipeptide HIV protease inhibitor ($K_i = 0.33$ nM) with strong activity against a wide spectrum of HIV-1 strains and isolates *in vitro* such as lymphotropic HIV-1_{LAI} and macrophage-tropic HIV-1_{Ba-L} in PHA-stimulated peripheral blood mononuclear cells ($IC_{50} = 44$ and 24 nM, respectively) and HIV-2_{EHO} in MT-2 cells ($IC_{50} = 47$ nM). Compound also showed potent activity against highly protease inhibitor-resistant clinical isolates of HIV-1 ($IC_{50} = 13-41$ nM) and the emergence of JE-2147-resistant strains was significantly slower than for KNI-272 and other protease inhibitors. Compound exhibited a favorable pharmacokinetic and safety profile in animals, with good oral bioavailability (37%) in dogs. Another compound within this series of peptidomimetic HIV protease inhibitors is:



JE-1520 [277044]^{1,3}: C33 H39 N3 O5 S

SOURCES – Agouron (Warner-Lambert); Japan Energy.

REFERENCES

1. Kato, R. et al. (Japan Energy Corp.) *HIV-protease inhibitors*. CA 2179935, EP 751145, JP 98025242.

2. Kiso, Y. *Design and synthesis of a covalently linked HIV-1 protease dimer analog and peptidomimetic inhibitors*. Yuki Gosei Kagaku Kyokaiishi 1998, 56(11): 896.

3. Mimoto, T. et al. *Structure-activity relationship of small-sized HIV protease inhibitors containing allophenylnorstatine*. J Med Chem 1999, 42(10): 1789.

4. Nash-Alexander, T. et al. *Determination of the in vitro resistance profile of AG1776, a novel inhibitor of HIV protease*. Antivir Ther 1999, 4(Suppl. 1): Abst 19.

5. Patick, A.K. et al. *Antiviral activity and resistance profile of AG1776, a novel inhibitor of HIV-1 protease*. 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb 4, Chicago) 1999, Abst 11.

6. Sato, H. et al. *In vitro antiviral effects of JE-2147, a novel HIV protease inhibitor, and its pharmacokinetics*. 12th Congr Jpn Soc AIDS Res (Dec 1-2, Tokyo) 1998, Abst 111.

7. Ueno, T. et al. *Anti-HIV-1 activity of and HIV-1 resistance profiles against JE-2147 (KNI-764), a novel inhibitor of HIV-1 protease*. 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12270.

8. Ueno, T. et al. *Pharmacokinetics and oral bioavailability of a novel HIV protease inhibitor JE-2147 (KNI-764) in animals*. 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 42273.

9. Yoshimura, K. et al. *JE-2147: A dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1*. Proc Natl Acad Sci USA 1999, 96(15): 8675.

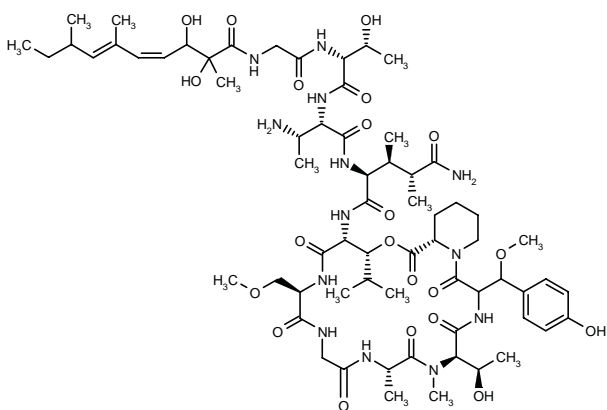
10. Agouron acquires new HIV protease inhibitor from Japan Energy Corporation. Agouron Pharmaceuticals, Inc. Press Release 1998, June 30.

11. Agouron R&D products will round out Warner-Lambert's pipeline. DailyDrugNews.com (Daily Essentials) 1999, Jan 29.

PAPUAMIDE A

278348

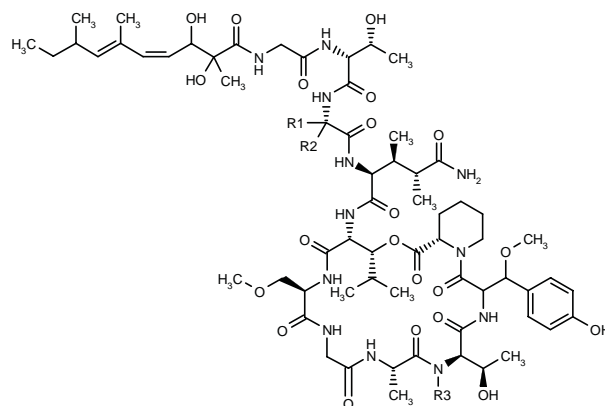
(6*R*,9*S*,15*R*,18*R*,19*R*,22*S*)-18-[2(*S*)-[3(*S*)-Amino-2(*S*)-[2(*R*)-[2-[2,3-dihydroxy-2,6,8-trimethyldeca-4(*Z*),6(*E*)-dienamido]acetamido]-3(*R*)-hydroxybutyramido]-butyramido]-4(*R*)-carbamoyl-3(*S*)-methylpentanamido]-6-[1(*R*)-hydroxyethyl]-3-[1-(4-hydroxyphenyl)-1-methoxymethyl]-19-isopropyl-15-(methoxymethyl)-7,9-dimethyl-20-oxa-1,4,7,10,13,16-hexaazabicyclo[20.4.0]hexacosane-2,5,8,11,14,17,21-heptaone



C₆₆ H₁₀₅ N₁₃ O₂₁; Mol wt: 1416.6250

$[\alpha]_D^{25} +12^\circ$ (c 3.47, MeOH).

ACTION—Anti-HIV and cytotoxic agent extracted from the sponges *Theonella mirabilis* and *Theonella swinhoei*, proven to inhibit HIV-1_{RF} replication in human T-lymphoblastoid cells (EC₅₀ = 3.6 ng/ml) and to have relatively low cytotoxicity IC₅₀ = 74 ng/ml). Compound was cytotoxic against a panel of human cancer cell lines, with a mean IC₅₀ of 75 ng/ml. Other compounds from the same source are:



Compound	R1	R2	R3	Formula
Papuamide B [278349]	H	(S)-CH(Me)NH ₂	H	C ₆₅ H ₁₀₃ N ₁₃ O ₂₁
Papuamide C [278350]		-CH(Me)-	Me	C ₆₆ H ₁₀₂ N ₁₂ O ₂₁
Papuamide D [278351]		-CH(Me)-	H	C ₆₅ H ₁₀₀ N ₁₂ O ₂₁

SOURCES—University of British Columbia, Vancouver, BC (CA); National Cancer Institute, Bethesda, MD (US).

REFERENCES

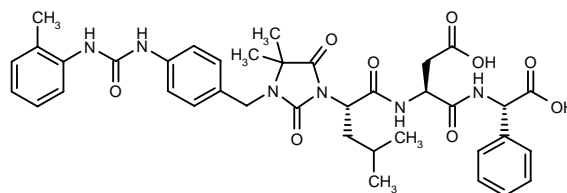
- Ford, P.W. et al. *Papuamides A - D, HIV-inhibitory and cytotoxic depsipeptides from the sponges Theonella mirabilis and Theonella swinhoei collected in Papua New Guinea*. J Am Chem Soc 1999, 121(25): 5899.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

276844

N-[2(*S*)-[4,4-Dimethyl-3-[4-[3-(2-methylphenyl)ureido]-benzyl]-2,5-dioximidazolidin-1-yl]-4-methylpentanoyl]-L-aspartyl-L-phenylglycine



C₃₈ H₄₄ N₆ O₉; Mol wt: 728.7986

ACTION—Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration and/or disorders involving adhesion processes mediated by the VLA-4 receptor such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the CNS, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, cancer and malaria. Compound was found to inhibit the adhesion of U937 cells to hVCAM-1(1-3)-IgG with an IC₅₀ value of 0.85 nM. Other compounds from this series of substituted imidazolidine derivatives include the following:

5. Patick, A.K. et al. *Antiviral activity and resistance profile of AG1776, a novel inhibitor of HIV-1 protease*. 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb 4, Chicago) 1999, Abst 11.

6. Sato, H. et al. *In vitro antiviral effects of JE-2147, a novel HIV protease inhibitor, and its pharmacokinetics*. 12th Congr Jpn Soc AIDS Res (Dec 1-2, Tokyo) 1998, Abst 111.

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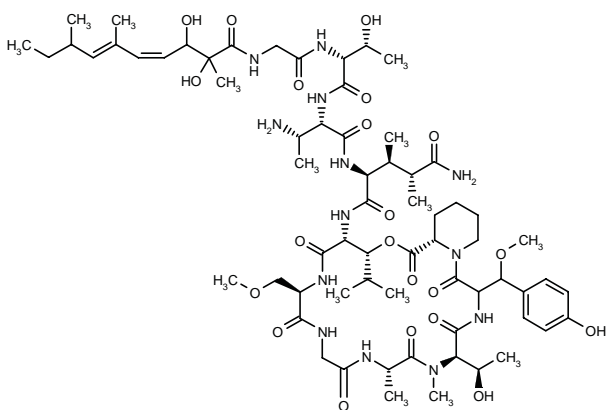
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PAPUAMIDE A

278348

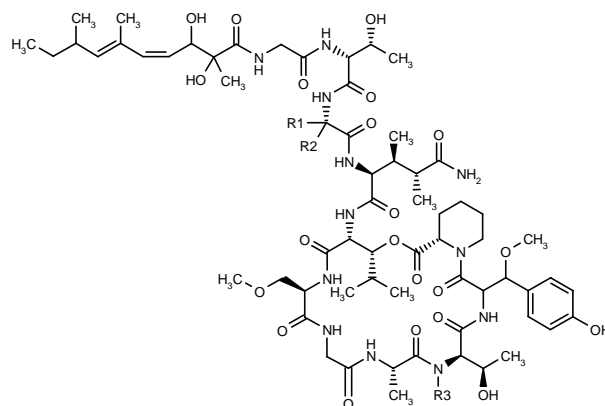
(6*R*,9*S*,15*R*,18*R*,19*R*,22*S*)-18-[2(*S*)-[3(*S*)-Amino-2(*S*)-[2(*R*)-[2-[2,3-dihydroxy-2,6,8-trimethyldeca-4(*Z*),6(*E*)-dienamido]acetamido]-3(*R*)-hydroxybutyramido]-butyramido]-4(*R*)-carbamoyl-3(*S*)-methylpentanamido]-6-[1(*R*)-hydroxyethyl]-3-[1-(4-hydroxyphenyl)-1-methoxymethyl]-19-isopropyl-15-(methoxymethyl)-7,9-dimethyl-20-oxa-1,4,7,10,13,16-hexaazabicyclo[20.4.0]hexacosane-2,5,8,11,14,17,21-heptaone



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$[\alpha]_D^{25} +12^\circ$ (c 3.47, MeOH).

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Papuamide C [278350]		-CH(Me)-	Me	C ₆₆ H ₁₀₂ N ₁₂ O ₂₁
Papuamide D [278351]		-CH(Me)-	H	C ₆₅ H ₁₀₀ N ₁₂ O ₂₁

SOURCES—University of British Columbia, Vancouver, BC (CA); National Cancer Institute, Bethesda, MD (US).

REFERENCES

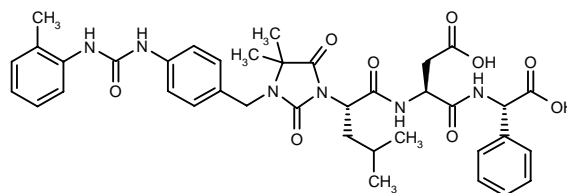
- Ford, P.W. et al. *Papuamides A - D, HIV-inhibitory and cytotoxic depsipeptides from the sponges Theonella mirabilis and Theonella swinhoei collected in Papua New Guinea*. J Am Chem Soc 1999, 121(25): 5899.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

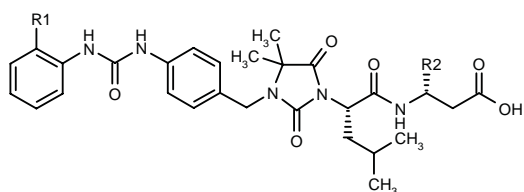
276844

N-[2(*S*)-[4,4-Dimethyl-3-[4-[3-(2-methylphenyl)ureido]-benzyl]-2,5-dioximidazolidin-1-yl]-4-methylpentanoyl]-L-aspartyl-L-phenylglycine



C₃₈ H₄₄ N₆ O₉; Mol wt: 728.7986

ACTION—Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration and/or disorders involving adhesion processes mediated by the VLA-4 receptor such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the CNS, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, cancer and malaria. Compound was found to inhibit the adhesion of U937 cells to hVCAM-1(1-3)-IgG with an IC₅₀ value of 0.85 nM. Other compounds from this series of substituted imidazolidine derivatives include the following:



Compound	R1	R2	Formula
276845	Me	1,3-benzodioxol-5-yl	C ₃₆ H ₄₁ N ₅ O ₈
276846	Me	Ph	C ₃₅ H ₄₁ N ₅ O ₆
276847	F	(S)-(2-Ph)-Gly-OH	C ₃₇ H ₄₁ FN ₅ O ₉
276848	Me	CO-L-Val-L-Pro-OH	C ₄₀ H ₅₃ N ₇ O ₁₀
276850	Me	(F)5-Ph	C ₃₅ H ₃₆ F ₅ N ₅ O ₆
276851	Me	2,4-(MeO)2-Ph	C ₃₇ H ₄₅ N ₅ O ₈

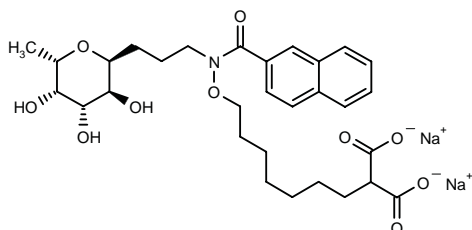
SOURCE – Hoechst Marion Roussel.

REFERENCES

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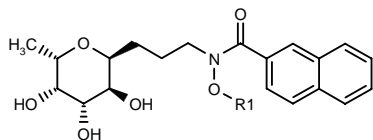
278527

2-[7-[N-[3-(6-Deoxy-α-L-galactopyranosyl)propyl]-N-(2-naphthylcarbonyl)aminoxy]heptyl]malonic acid disodium salt



C30 H39 N Na2 O10; Mol wt: 619.6151

ACTION – Agent for the treatment of inflammation, cancer, autoimmune diseases and ischemia-reperfusion injury, an inhibitor of P- and L-selectin. Other compounds from this series of hydroxylamine derivatives include the following:



Compound	R1	Formula
278528	(CH ₂) ₈ CH(CO ₂ Na) ₂	C ₃₁ H ₄₁ NNa ₂ O ₁₀
278529	H	C ₂₀ H ₂₅ NO ₆
278530	(CH ₂) ₃ CO ₂ Na	C ₂₄ H ₃₀ NNaO ₈

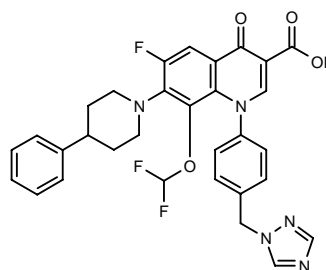
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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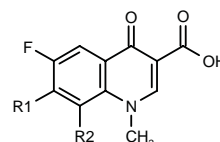
278558

8-(Difluoromethoxy)-6-fluoro-4-oxo-7-(4-phenyl-1-piperidinyl)-1-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-1,4-dihydroquinoline-3-carboxylic acid



C31 H26 F3 N5 O4; Mol wt: 589.5714

ACTION – Cytokine production inhibitor proven active in inhibiting phytohemagglutinin-stimulated IL-6 and TNF-α production in human peripheral blood monocytes at 0.8 μM. Within this series of 1,4-dihydroquinoline derivatives, the following are also included:



Compound	R1	R2	Formula
278559	4-Ph-1,2,3,6-tetrahydro-1-Pyr	CF ₃	C ₂₃ H ₁₈ F ₄ N ₂ O ₃
278560	4-(2-MeO-Ph)-1-Piz	CH ₂ N(Me) ₂	C ₂₅ H ₂₉ FN ₄ O ₄

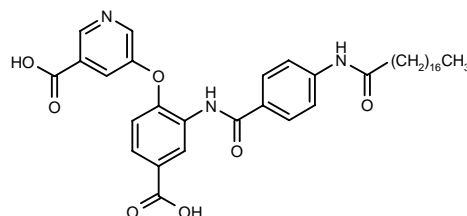
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Baba, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *Cytokine production inhibitors*. JP 99158071.

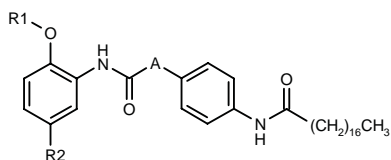
279082

5-[4-Carboxy-2-[4-(octadecanamido)benzamido]-phenoxy]pyridine-3-carboxylic acid



C38 H49 N3 O7; Mol wt: 659.8191

ACTION – Antiinflammatory agent, an inhibitor of E-selectin (IC₅₀ = 19 μM), P-selectin (IC₅₀ = 11 μM) and L-selectin (IC₅₀ = 4.2 μM) binding. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
279083	3-CO ₂ H-Ph	CO ₂ H	bond	C ₃₉ H ₅₀ N ₂ O ₇
279084	3-CO ₂ H-Ph	CO ₂ H	-(CH ₂) ₂ -	C ₄₁ H ₅₄ N ₂ O ₇
279085	3-CO ₂ H-Ph	CO ₂ H	-CH ₂ -	C ₄₀ H ₅₂ N ₂ O ₇
279086	3-CO ₂ H-Ph	H	bond	C ₃₈ H ₅₀ N ₂ O ₅
279087	Ph	CO ₂ H	bond	C ₃₈ H ₅₀ N ₂ O ₅
279088	4-CO ₂ H-Ph	CO ₂ H	bond	C ₃₉ H ₅₀ N ₂ O ₇
279089	(CH ₂) ₃ CO ₂ H	CO ₂ H	bond	C ₃₆ H ₅₂ N ₂ O ₇

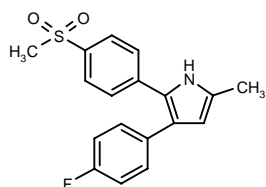
SOURCE – Kanebo.

REFERENCES

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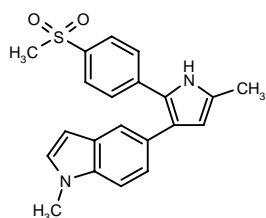
279226

3-(4-Fluorophenyl)-5-methyl-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole



C18 H16 F N O₂ S; Mol wt: 329.3934

ACTION – Antiinflammatory and antineoplastic agent with selective cyclooxygenase type 2 (COX-2)-inhibitory activity *in vitro* (IC₅₀ = 0.95 μM vs. 649.0 μM for COX-1). *In vivo*, compound inhibited carrageenan-induced rat paw edema by 35.5% at 10 mg/kg p.o. and was found to be equipotent to indomethacin in an adjuvant-induced arthritis model in rats while exhibiting higher analgesic activity in a rat model at 3 mg/kg p.o. Contrary to indomethacin, compound was free of gastric ulcerogenic effects at doses up to 1000 mg/kg p.o. In addition, it was shown to inhibit the proliferation of colorectal carcinoma Caco-2 cells (IC₅₀ = 0.78 μM vs. 3.30 μM for 5-fluorouracil), to induce apoptosis in Caco-2 cells at 1 μM and to inhibit tumor growth *in vivo* in mice bearing sarcoma 180 tumors at 10 mg/kg/day i.p. x 10 days. No signs of toxicity were observed following a single administration of up to 2000 mg/kg p.o. or 100 mg/kg/day p.o. x 14 days to rats. Another compound from this series of 5-arylpyrrole derivatives is:



279227: C₂₁ H₂₀ N₂ O₂ S

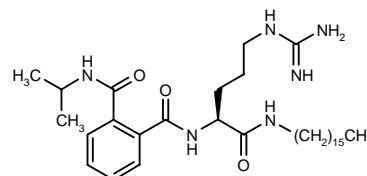
SOURCE – Nissin Food Products.

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1. Yamada, T. et al. (Nissin Food Products Co., Ltd.) *5-Arylpyrrole derivs.* WO 9933796.

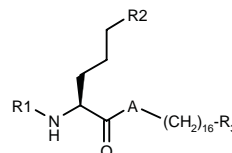
279432

*N*¹-Hexadecyl-*N*²-[2-(*N*-isopropylcarbamoyl)benzoyl]-L-argininamide



C₃₃ H₅₈ N₆ O₃; Mol wt: 586.8602

ACTION – Chemokine receptor antagonist proven to inhibit [¹²⁵I]-IL-8, [¹²⁵I]-RANTES and [¹²⁵I]-SDF-1 binding in human THP-1 cells by 90, 80 and 80%, respectively, at a concentration of 100 μM. No mortality was observed following oral administration of 500 mg/kg to mice. Within this series of amino acid derivatives, the following are also included:



Compound	R1	R2	R3	A	Formula
279433	i-BuCH ₂ CO	NHC(=NH)NH ₂	Et	O	C ₃₀ H ₆₀ N ₄ O ₃
279434	3-(i-PrNHCO)-PhCO	CH ₂ NH ₂	H	NH	C ₃₃ H ₅₈ N ₄ O ₃
279435	Ac-L-Leu-L-Arg-	NH ₂	Et	O	C ₃₇ H ₇₃ N ₇ O ₅

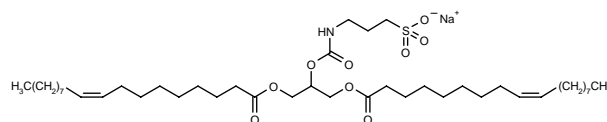
SOURCE – Kureha.

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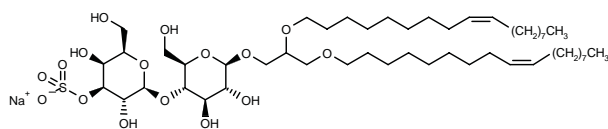
279456

3-[2-[9(*Z*)-Octadecenoyloxy]-1-[9(*Z*)-octadecenoyloxy-methyl]ethoxycarbonylamino]-1-propanesulfonic acid sodium salt

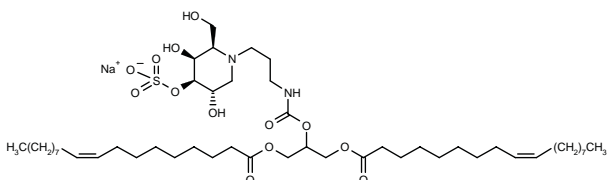


C₄₃ H₇₈ N Na O₉ S; Mol wt: 808.1432

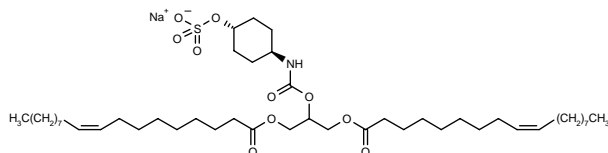
ACTION – Antiinflammatory agent, a cell adhesion inhibitor shown to inhibit P- and L-selectin binding with IC₅₀ values of 0.04 μM, as well as to inhibit lipopolysaccharide-stimulated TNF-α production in human monocytic leukemia THP-1 cells (80.5% inhibition at 30 μg/ml). Within this series of double-chain aliphatic derivatives, the following are also included:



279457: C51 H95 Na O16 S



279458: C49 H89 N2 Na O13 S



279459: C46 H82 N Na O10 S

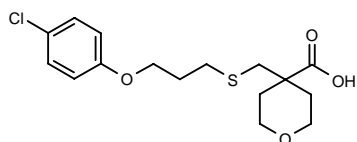
SOURCE – Nippon Shinyaku.

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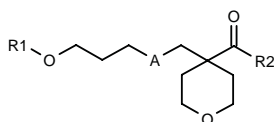
279877

4-[3-(4-Chlorophenoxy)propylsulfanylmethyl]tetrahydropyran-4-carboxylic acid



C16 H21 Cl O4 S; Mol wt: 344.8569

ACTION – Matrix metalloproteinase (MMP) and TNF- α production inhibitor reported to inhibit stromelysin, collagenase and gelatinase activity *in vitro* and which may also inhibit MMP-mediated membrane shedding events. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis and metastatic tumors, among other conditions. Other specifically claimed hydroxamic and carboxylic acid derivatives are:



Compound	R1	R2	A	Formula
279878	4-Cl-Ph	NHOH	SO2	C ₁₈ H ₂₂ ClNO ₆ S
279879	4-MeO-Ph	OMe	S	C ₁₈ H ₂₆ O ₅ S
279880	3-Pyr	OMe	S	C ₁₆ H ₂₃ NO ₄ S
279882	4-MeO-Ph	OH	SO2	C ₁₇ H ₂₄ O ₇ S

SOURCE – Darwin Discovery.

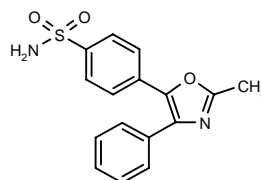
REFERENCES

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SC-299

279180

4-(2-Methyl-4-phenyloxazol-5-yl)benzenesulfonamide



C16 H14 N2 O3 S; Mol wt: 314.3636

ACTION – Potent human cyclooxygenase type 2 (hCOX-2) inhibitor (IC₅₀ = 0.027 μ M) with at least 800-fold selectivity over hCOX-1 (IC₅₀ = 21.4 μ M); it almost completely reduced prostaglandin production in the inflammatory air pouch model in rats (ED₅₀ = 0.94 mg/kg p.o.). Compound exhibited potent activity in the carrageenan-induced paw edema model in rats (ED₅₀ = 10 mg/kg p.o.) and in a hyperalgesia model of inflammatory pain (ED₅₀ = 17 mg/kg p.o.), as well as against adjuvant-induced arthritis in rats (ED₅₀ = 0.62 mg/kg p.o.). Potentially useful for the treatment of acute and chronic inflammatory diseases.

SOURCE – Searle.

REFERENCES

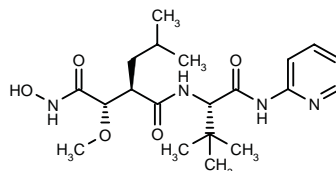
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3. Seibert, K. et al. (G.D. Searle & Co.) *Method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia.* WO 9816227.
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SOLIMASTAT

Prop INN

275829

*N*¹-[2,2-Dimethyl-1(*S*)-[*N*-(2-pyridyl)carbamoyl]propyl]-*N*⁴-hydroxy-2(*R*)-isobutyl-3(*S*)-methoxysuccinamide



C20 H32 N4 O5; Mol wt: 408.4958

ACTION – Matrix metalloproteinase (MMP) inhibitor with potential advantages over other MMP inhibitors due to its reduced tendency to cause painful musculoskeletal side effects and its good oral bioavailability. Based on these characteristics, solimastat is expected to have a relatively wide therapeutic window, making it appropriate for medium- or long-term administration in the treatment of cancer, rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome or psoriasis.

SOURCE – British Biotech.

REFERENCES

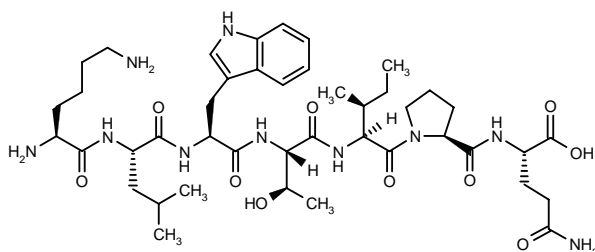
1. Beckett, R.P. et al. (British Biotech plc) *Metalloproteinase inhibitors*. GB 2333524, WO 9925693.

2. *Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 276.

IMMUNOMODULATING AGENTS

276575

L-Lysyl-L-leucyl-L-tryptophyl-L-threonyl-L-isoleucyl-L-prolyl-L-glutamine



C43 H68 N10 O10; Mol wt: 885.0702

ACTION – Peptide with high affinity for IL-6, a representative compound from a series of peptides acting as IL-6 agonists and antagonists.

Agonists may be useful as immunostimulants and for increasing hematopoiesis, and antagonists may be useful for the treatment of autoimmune diseases, myeloma and osteoporosis.

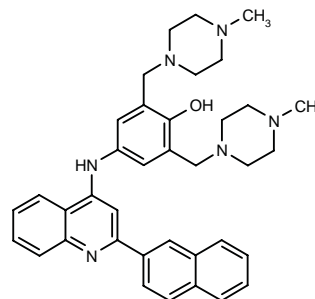
SOURCE – Tosoh.

REFERENCES

1. Imanaka, T. et al. (Tosoh Corporation) *Peptide which binds specifically to IL-6*. JP 99092498.

278080

N-[4-Hydroxy-3,5-bis(4-methylpiperazin-1-ylmethyl)-phenyl]-2-(2-naphthyl)quinoline-4-amine



C37 H42 N6 O; Mol wt: 586.7798

ACTION – An antagonist of immunostimulatory CpG-oligodeoxynucleotides (CpG-ODN) proven to inhibit CpG-ODN-induced thymidine uptake by WEHI 231 B-cells in the presence of α -slgM with an EC_{50} value of 0.24 nM. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

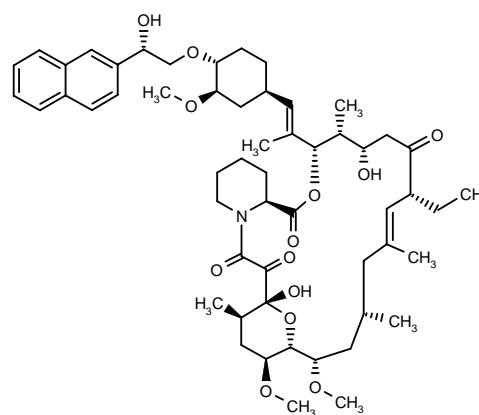
SOURCES – Georgia State University, Atlanta, GA (US); University of Iowa, Iowa City, IA (US).

REFERENCES

1. Strekowski, L. et al. *Structure-activity relationship analysis of substituted 4-quinolinamines, antagonists of immunostimulatory CpG-oligodeoxynucleotides*. Bioorg Med Chem Lett 1999, 9(13): 1819.

278884

(1*R*,9*S*,12*S*,13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*)-17-Ethyl-1,14-dihydroxy-23,25-dimethoxy-12-[2-[4(*R*)-[2(*S*)-hydroxy-2-(2-naphthyl)ethoxy]-3(*R*)-methoxycyclohex-1(*R*)-yl]-1(*E*)-methylvinyl]-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetrone



C55 H79 N O13; Mol wt: 962.2231

ACTION – Matrix metalloproteinase (MMP) inhibitor with potential advantages over other MMP inhibitors due to its reduced tendency to cause painful musculoskeletal side effects and its good oral bioavailability. Based on these characteristics, solimastat is expected to have a relatively wide therapeutic window, making it appropriate for medium- or long-term administration in the treatment of cancer, rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome or psoriasis.

SOURCE – British Biotech.

REFERENCES

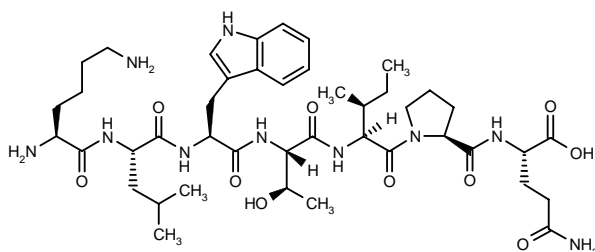
1. Beckett, R.P. et al. (British Biotech plc) *Metalloproteinase inhibitors*. GB 2333524, WO 9925693.

2. *Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 276.

IMMUNOMODULATING AGENTS

276575

L-Lysyl-L-leucyl-L-tryptophyl-L-threonyl-L-isoleucyl-L-prolyl-L-glutamine



C43 H68 N10 O10; Mol wt: 885.0702

ACTION – Peptide with high affinity for IL-6, a representative compound from a series of peptides acting as IL-6 agonists and antagonists.

Agonists may be useful as immunostimulants and for increasing hematopoiesis, and antagonists may be useful for the treatment of autoimmune diseases, myeloma and osteoporosis.

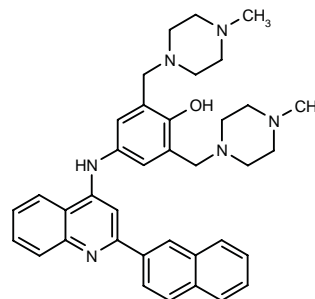
SOURCE – Tosoh.

REFERENCES

1. Imanaka, T. et al. (Tosoh Corporation) *Peptide which binds specifically to IL-6*. JP 99092498.

278080

N-[4-Hydroxy-3,5-bis(4-methylpiperazin-1-ylmethyl)-phenyl]-2-(2-naphthyl)quinoline-4-amine



C37 H42 N6 O; Mol wt: 586.7798

ACTION – An antagonist of immunostimulatory CpG-oligodeoxynucleotides (CpG-ODN) proven to inhibit CpG-ODN-induced thymidine uptake by WEHI 231 B-cells in the presence of α -slgM with an EC_{50} value of 0.24 nM. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

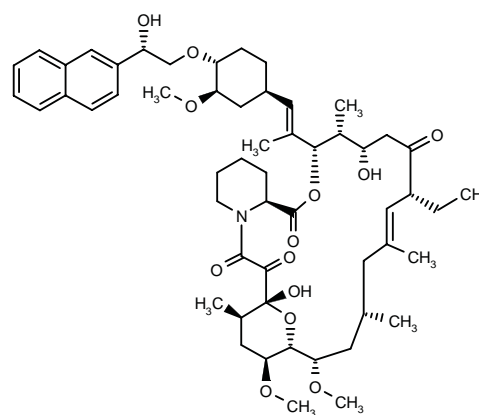
SOURCES – Georgia State University, Atlanta, GA (US); University of Iowa, Iowa City, IA (US).

REFERENCES

1. Strekowski, L. et al. *Structure-activity relationship analysis of substituted 4-quinolinamines, antagonists of immunostimulatory CpG-oligodeoxynucleotides*. Bioorg Med Chem Lett 1999, 9(13): 1819.

278884

(1*R*,9*S*,12*S*,13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*)-17-Ethyl-1,14-dihydroxy-23,25-dimethoxy-12-[2-[4(*R*)-[2(*S*)-hydroxy-2-(2-naphthyl)ethoxy]-3(*R*)-methoxycyclohex-1(*R*)-yl]-1(*E*)-methylvinyl]-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetron



C55 H79 N O13; Mol wt: 962.2231

ACTION – Immunosuppressant, an ascomycin derivative that acts as a potent inhibitor of T-cell proliferation *in vitro* (IC_{50} = 0.33 nM), binds to the cytosolic FKBP-12 protein (EC_{50} = 21.1 nM) and inhibits the activity of the serine/threonine phosphatase calcineurin (IC_{50} = 2.8 nM). *In vivo*, compound inhibited splenic T-cell proliferation in mice after both i.v. and p.o. administration (ED_{50} = 0.38 and 3.7 mg/kg, respectively). Compared to FK-506, compound showed an improved therapeutic index, with at least 3-fold less acute and chronic nephrotoxicity.

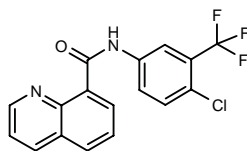
SOURCE – Merck & Co.

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- Armstrong, H.M. et al. *Potent immunosuppressive C32-O-arylethyl ether derivatives of ascomycin with reduced toxicity*. Bioorg Med Chem Lett 1999, 9(14): 2089.

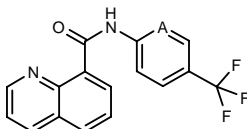
279939

N-[4-Chloro-3-(trifluoromethyl)phenyl]quinoline-8-carboxamide



C17 H10 Cl F3 N2 O; Mol wt: 350.7260

ACTION – B-cell activation inhibitor (IC_{50} = 1.7 μ M against antigen-induced murine T-cell-independent B-cell IgM antibody production) devoid of inhibitory activity against dihydroorotate dehydrogenase (IC_{50} > 50 μ M). It also inhibited T-cell-independent antibody formation *in vivo* in mice by 90% at a dose of 30 mg/kg s.c. and was able to protect hamster heart xenografts from humoral rejection in nude mice at a dose of 10 mg/kg/day i.p. Other exemplified compounds are:



Compound	A	Formula
279940	CH	C ₁₇ H ₁₁ F ₃ N ₂ O
279941	N	C ₁₆ H ₁₀ F ₃ N ₃ O

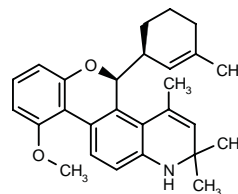
SOURCE – Novartis.

REFERENCES

- Albert, R. et al. (Novartis AG) *B cell inhibitors*. WO 9941239.

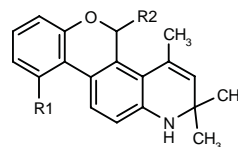
280004

(-)-10-Methoxy-5(*S*)-[3-methylcyclohex-2-en-1(*S*)-yl]-2,2,4-trimethyl-2,5-dihydro-1*H*-1-benzopyrano[3,4-*f*]-quinoline



C27 H31 N O2; Mol wt: 401.5469

ACTION – Agent for the treatment of immune, autoimmune and inflammatory diseases with high affinity and selectivity for the human glucocorticoid receptor (GR- α ; IC_{50} = 0.7 nM) relative to the human progesterone receptor (PR-A; IC_{50} = 10,000 nM). Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
280010	OMe	Ph	racemic	C ₂₆ H ₂₅ NO ₂
280011	Et	Ph		C ₂₇ H ₂₇ NO
280013	ethynyl-CH ₂ O	Ph		C ₂₈ H ₂₅ NO ₂
280015	OMe	3-(cyclopropyl-CH ₂ O)-Ph		C ₃₀ H ₃₁ NO ₃
280016	OMe	(R)-3-(CH ₂ OH)-2-cyclohexenyl	(-)-(S)	C ₂₇ H ₃₁ NO ₃

SOURCES – Abbott; Ligand.

REFERENCES

- Coughlan, M.J. et al. (Abbott Laboratories Inc.; Ligand Pharmaceuticals, Inc.) *Glucocorticoid-selective anti-inflammatory agents*. WO 9941256.

L-3002^{2-4,6}

278734

Liposome-encapsulated JBT-3002

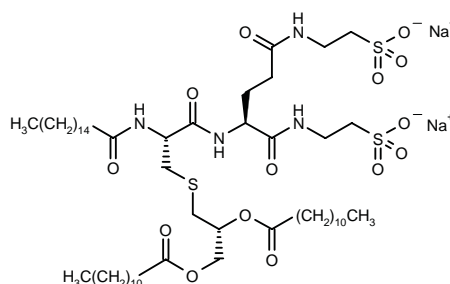
Liposomal JBT-3002

JBT-3002¹⁻⁶

259670

S-[2(*R*),3-Bis(dodecanoyloxy)propyl]-*N*-(hexadecanoyl)-L-cysteinyl-L-glutamic acid *N*¹,*N*⁵-bis(2-sulfoethyl)amide disodium salt

CGP-40774



C55 H102 N4 Na2 O14 S3 ; Molt wt: 1185.6030

ACTION – Liposome-encapsulated formulation of the immunomodulating agent JBT-3002, an orally active macrophage activator able to stimulate the production and release of growth factors from macrophages, subsequently producing an increase in the production of platelets and neutrophils in bone marrow. Compound activates macrophages surrounding blood vessels of the respiratory, gastrointestinal and urogenital tracts, providing a defense against microorganisms and parasites. It was also seen to activate tumoricidal properties of monocytes and macrophages against human osteogenic sarcoma lung metastases in nude mice. Orally administered free compound was also able to delay the growth of human pancreatic cancer and protect against lymph node metastasis when administered to athymic nude mice in combination with the chemotherapeutic CPT-11 (irinotecan). Potentially useful for the treatment of both cancer and the myelosuppression secondary to chemotherapy.

SOURCE – Jenner.

REFERENCES

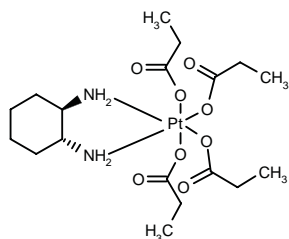
1. Baschang, G. and Hartmann, A. (Ciba-Geigy AG) *Aminosulphonic acid derivs. and process for their preparation*. EP 548024, JP 93255239, US 5342977.
2. Spittler, L.E. and Fidler, I.J. (Jenner Biotherapies, Inc.) *Therapeutic liposome-encapsulated immunomodulators*. WO 9935162.
3. Bruns, C.J. et al. *Eradication of human pancreatic cancer lymph node metastasis by irinotecan and the immunomodulator JBT3002*. Proc Amer Assoc Cancer Res 1999, 40: Abst 2272.
4. Eue, I. et al. *Induction of nitric oxide production and tumoricidal properties in murine macrophages by a new synthetic lipopeptide JBT3002 encapsulated in liposomes*. J Immunother 1998, 21(5): 340.
5. Shinohara, H. et al. *Oral administration of the immunomodulator JBT-3002 induces endogenous interleukin 15 in intestinal macrophages for protection against irinotecan-mediated destruction of intestinal epithelium*. Clin Cancer Res 1999, 5(8): 2148.
6. Worth, L.L. et al. *Eradication of experimental osteosarcoma pulmonary metastases by systemic administration of liposomes containing the new synthetic lipopeptide JBT 3002*. Proc Amer Assoc Cancer Res 1998, 39: Abst 3604.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

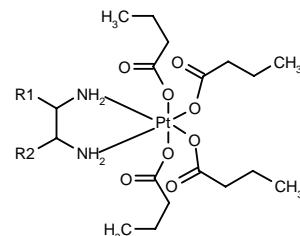
278763

Tetrakis(propionato)[*trans*-(±)-cyclohexane-1,2-diamine]-platinum(IV)

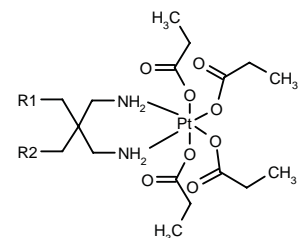


C18 H34 N2 O8 Pt; Mol wt: 601.5526

ACTION – Antineoplastic agent, a platinum complex with good oral activity due to its improved absorption in the gastrointestinal tract relative to known platinum complexes, resulting from its high lipophilicity; it also shows low toxicity. When administered orally at 150 mg/kg to mice bearing L1210 leukemia, it increased survival, giving a T/C x 100 value of 160.9%. Other exemplified compounds from this series of platinum(IV) complexes include the following:



Compound	R1	R2	Formula
278765	-(CH2)4-		C ₂₂ H ₄₂ N ₂ O ₈ Pt
278766	H	H	C ₁₈ H ₃₆ N ₂ O ₈ Pt



Compound	R1	R2	Formula
278767	H	H	C ₁₇ H ₃₄ N ₂ O ₈ Pt
278768	-(CH2)3-		C ₂₀ H ₃₈ N ₂ O ₈ Pt

SOURCE – Korea Institute of Science and Technology, Seoul (KR).

REFERENCES

1. Sohn, Y.S. et al. (Korea Institute of Science and Technology) *Anticancer platinum (IV) complexes for oral administration*. WO 9933782.

ANTIMETABOLITES

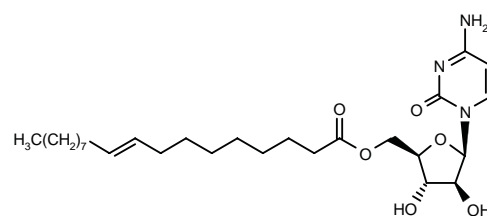
P-4055

278822

5'-O-[9(*E*)-Octadecenoyl]-1-β-D-arabinofuranosylcytosine

4-Amino-1-[5-O-[9(*E*)-octadecenoyl]-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone

Elaidic acid-cytarabine



C27 H45 N3 O6; Mol wt: 507.6675

ACTION – Liposome-encapsulated formulation of the immunomodulating agent JBT-3002, an orally active macrophage activator able to stimulate the production and release of growth factors from macrophages, subsequently producing an increase in the production of platelets and neutrophils in bone marrow. Compound activates macrophages surrounding blood vessels of the respiratory, gastrointestinal and urogenital tracts, providing a defense against microorganisms and parasites. It was also seen to activate tumoricidal properties of monocytes and macrophages against human osteogenic sarcoma lung metastases in nude mice. Orally administered free compound was also able to delay the growth of human pancreatic cancer and protect against lymph node metastasis when administered to athymic nude mice in combination with the chemotherapeutic CPT-11 (irinotecan). Potentially useful for the treatment of both cancer and the myelosuppression secondary to chemotherapy.

SOURCE – Jenner.

REFERENCES

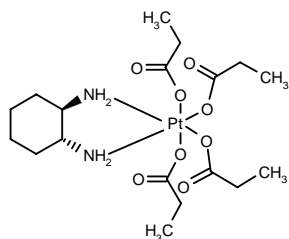
1. Baschang, G. and Hartmann, A. (Ciba-Geigy AG) *Aminosulphonic acid derivs. and process for their preparation*. EP 548024, JP 93255239, US 5342977.
2. Spittler, L.E. and Fidler, I.J. (Jenner Biotherapies, Inc.) *Therapeutic liposome-encapsulated immunomodulators*. WO 9935162.
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5. Shinohara, H. et al. *Oral administration of the immunomodulator JBT-3002 induces endogenous interleukin 15 in intestinal macrophages for protection against irinotecan-mediated destruction of intestinal epithelium*. Clin Cancer Res 1999, 5(8): 2148.
6. Worth, L.L. et al. *Eradication of experimental osteosarcoma pulmonary metastases by systemic administration of liposomes containing the new synthetic lipopeptide JBT 3002*. Proc Amer Assoc Cancer Res 1998, 39: Abst 3604.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

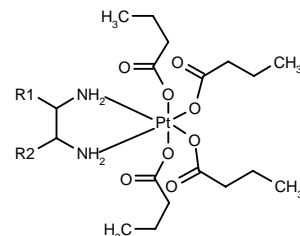
278763

Tetrakis(propionato)[*trans*-(±)-cyclohexane-1,2-diamine]-platinum(IV)

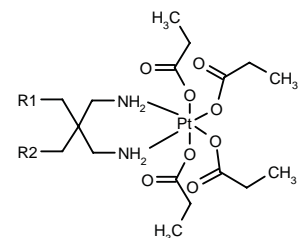


C18 H34 N2 O8 Pt; Mol wt: 601.5526

ACTION – Antineoplastic agent, a platinum complex with good oral activity due to its improved absorption in the gastrointestinal tract relative to known platinum complexes, resulting from its high lipophilicity; it also shows low toxicity. When administered orally at 150 mg/kg to mice bearing L1210 leukemia, it increased survival, giving a T/C x 100 value of 160.9%. Other exemplified compounds from this series of platinum(IV) complexes include the following:



Compound	R1	R2	Formula
278765	-(CH2)4-		C ₂₂ H ₄₂ N ₂ O ₈ Pt
278766	H	H	C ₁₈ H ₃₆ N ₂ O ₈ Pt



Compound	R1	R2	Formula
278767	H	H	C ₁₇ H ₃₄ N ₂ O ₈ Pt
278768	-(CH2)3-		C ₂₀ H ₃₈ N ₂ O ₈ Pt

SOURCE – Korea Institute of Science and Technology, Seoul (KR).

REFERENCES

1. Sohn, Y.S. et al. (Korea Institute of Science and Technology) *Anticancer platinum (IV) complexes for oral administration*. WO 9933782.

ANTIMETABOLITES

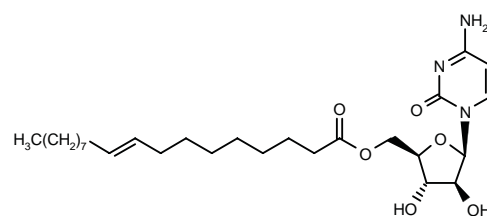
P-4055

278822

5'-O-[9(*E*)-Octadecenoyl]-1-β-D-arabinofuranosylcytosine

4-Amino-1-[5-O-[9(*E*)-octadecenoyl]-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone

Elaidic acid-cytarabine



C27 H45 N3 O6; Mol wt: 507.6675

ACTION – Antineoplastic agent, an elaidic acid ester of the nucleoside antimetabolite cytarabine with cytotoxic activity against a range of tumor cell lines including murine leukemia L1210, human T-cell leukemia CEM and Molt-4 and human malignant melanoma THX (IC_{50} = 0.04, 0.07, 0.0009 and 0.23 μ M, respectively). Compound appeared to use an alternative mechanism of internalization in cells compared with cytarabine, as its activity was not reduced by inhibitors of nucleoside carrier-dependent transport. *In vivo*, at a dose of 25 mg/kg given in 4 weekly cycles by daily bolus i.v. injection for 5 days, it exhibited high efficacy, superior to cytarabine, against solid tumor xenografts including melanoma, lung adenocarcinoma, breast cancer and osteogenic sarcoma xenografts.

SOURCE – Norsk Hydro.

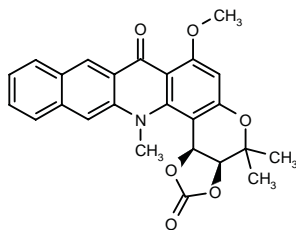
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1. Myhren, F. et al. (Norsk Hydro AS) *Improved therapeutic agents*. WO 9705154.
2. Bristol, K. et al. *Antitumor activity of P-4055 (elaidic acid-cytarabine) compared to cytarabine in metastatic and s.c. human tumor xenograft models*. Cancer Res 1999, 59(12): 2944.
3. Peters, G.J. et al. *Cell specific cytotoxicity and structure-activity relationship of lipophilic 1- β -D-arabinofuranosylcytosine (ara-C) derivatives*. Nucleosides Nucleotides 1999, 18(4-5): 877.

ANTIBIOTICS AND ALKALOIDS

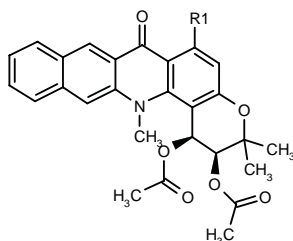
278583

cis-7-Methoxy-4,4,15-trimethyl-3a,8,15,15c-tetrahydro-4*H*-benzo[*b*][1,3]dioxolo[4',5':4,5]pyrano[3,2-*h*]acridine-2,8-dione

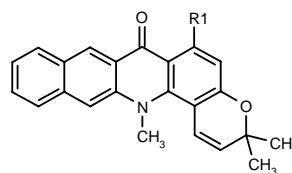


C25 H21 N O6; Mol wt: 431.4419

ACTION – Antineoplastic agent, a derivative of the alkaloid acronycine with improved activity, as demonstrated *in vitro* against murine leukemia L1210 cells (IC_{50} = 0.023 μ M vs. 27.0 μ M for acronycine) and *in vivo* in mice bearing murine leukemia P388, where it prolonged mean survival time with a T/C x 100 value of 327% at 12.5 mg/kg i.p. compared to a T/C x 100 value of 125% at 200 mg/kg i.p. for acronycine. Other specifically claimed compounds from this series of acronycine derivatives are:



Compound	R1	Isomer	Formula
278584	OMe	racemic	C ₂₆ H ₂₇ N ₂ O ₇
278587	NH(CH ₂) ₃ N(Et) ₂	racemic	C ₃₄ H ₄₁ N ₃ O ₆



Compound	R1	Formula
278585	OMe	C ₂₄ H ₂₁ NO ₃
278586	NH(CH ₂) ₃ N(Et) ₂	C ₃₀ H ₃₅ N ₃ O ₂

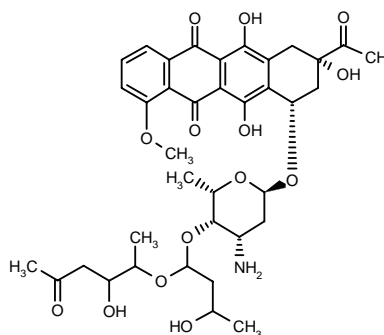
SOURCE – ADIR.

REFERENCES

1. Koch, M. et al. (ADIR et Cie.) *Novel acronycine derivs., preparation method and pharmaceutical compsns*. FR 2772765, WO 9932491.

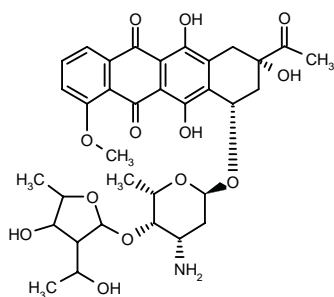
278850

4'-O-[3-Hydroxy-1-(2-hydroxy-1-methyl-4-oxopentyl)-butyl]daunomycin



C37 H47 N O14; Mol wt: 729.7713

ACTION – Antineoplastic agent, an anthracycline isolated from a culture of *Streptomyces peucetius* ATCC 27952 with more potent cytotoxicity against murine leukemia L1210 than the parent compound daunorubicin (IC_{50} = 0.085 μ g/ml vs. 0.259 μ g/ml for daunorubicin). Compound was also found to be more potent than doxorubicin against a panel of solid human tumor cell lines including mammary adenocarcinoma MCF-7, doxorubicin-resistant MCF-7, mammary adenocarcinoma MDA-MB-231, colon carcinoma HCT116 and ovarian carcinoma OVCAR-3 (IC_{50} = 15, 100, 0.03, 0.3 and 0.08 nM, respectively, vs. 940, > 10,000, 540, 80 and 140 nM, respectively, for doxorubicin). In addition, compound exhibited more potent antibacterial activity than daunorubicin, as demonstrated *in vitro* against *Staphylococcus aureus* ATCC 14154, *Bacillus subtilis* ATCC 6633 and *Micrococcus flavus* ATCC 10240 (MIC = 6.25, 1.56 and 1.56 μ g/ml, respectively, vs. 25, 3.12 and 6.25 μ g/ml, respectively, for daunorubicin). Another compound isolated from the same source is:



278851: C₃₄ H₄₁ N O₁₃

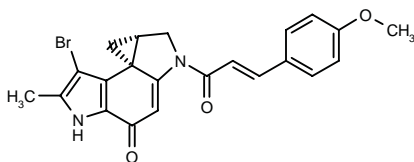
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Portello, C. et al. (Pharmacia & Upjohn SpA) *Anthracycline glycosides*. WO 9935153.

279025

(7b*R*,8a*S*)-7-Bromo-2-[3-(4-methoxyphenyl)-2(*E*)-propanoyl]-6-methyl-2,5,8,8a-tetrahydro-1*H*-cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-one



C₂₂ H₁₉ Br N₂ O₃; Mol wt: 439.3071

ACTION – Antineoplastic agent, a duocarmycin derivative with cytotoxic activity against human uterine cervical carcinoma HeLaS3 cells (IC₅₀ = 2.9 and 0.065 nM, respectively, after 1- and 72-h exposure). Compound showed excellent efficacy in reducing tumor volume in mice bearing human sarcoma 180 (T/C = 0.11 at 0.21 mg/kg i.v.) and human lung tumor LC-6 (T/C = 0.099 at 0.25 mg/kg i.v.), with low hematopoietic toxicity.

SOURCE – Kyowa Hakko.

REFERENCES

- Amishiro, N. et al. (Kyowa Hakko Kogyo Co., Ltd.) *DC-89 derivs*. WO 9809966.
- Amishiro, N. et al. *Synthesis and antitumor activity of duocarmycin derivatives: Modification of segment-A of A-ring pyrrole compounds*. J Med Chem 1999, 42(15): 2946.

NA-22598B₁

277524

ACTION – Antiproliferative agent isolated from *Streptomyces* sp. NA22598 (FERM P-14686) shown to inhibit the proliferation of human ovarian cancer A2780 cells and human colon cancer DLD1 cells with IC₅₀ values of 0.20 and 0.10 µg/ml, respectively. Another compound isolated from the same source is:

NA-22598B₂ [277525]

SOURCE – Nippon Kayaku.

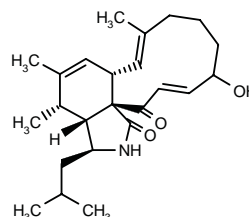
REFERENCES

1. Nishikiori, T. et al. (Nippon Kayaku Co., Ltd.) *Novel physiologically active substances NA22598B₁ and B₂, their preparation method and their use*. JP 99127881.

TMC-169

277753

(3*S*,3a*R*,4*S*,6a*S*)-12-Hydroxy-3-isobutyl-4,5,8-trimethyl-2,3,3a,4,6a,9,10,11,12,15-decahydro-1*H*-cycloundeca-[*d*]isoindole-1,15-dione



C₂₄ H₃₅ N O₃; Mol wt: 385.5445

M.p. 103-5 °C, [α]_D²³ -50°(c 0.31, MeOH).

ACTION – Antineoplastic antibiotic isolated from fungal strain *Aspergillus flavipes* TC 1446, with cytotoxicity against various tumor cell lines such as human histiocytic lymphoma U937 (IC₅₀ = 0.81 µM), Jurkat human lymphoma (IC₅₀ = 0.21 µM), human promyelocytic leukemia HL-60 (IC₅₀ = 0.68 µM), human colon adenocarcinoma WiDr (IC₅₀ = 0.83 µM) and human colon carcinoma HCT-116 (IC₅₀ = 0.78 µM).

SOURCE – Tanabe Seiyaku.

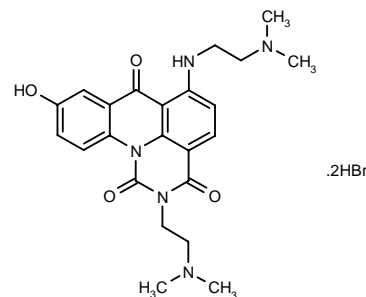
REFERENCES

1. Kohno, J. et al. *TMC-169, a new antibiotic of the aspochalasin group produced by Aspergillus flavipes*. J Antibiot 1999, 52(6): 575.

DNA-INTERCALATING DRUGS

278665

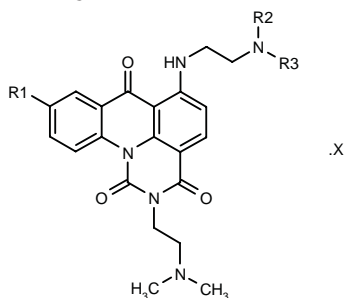
2-[2-(Dimethylamino)ethyl]-6-[2-(dimethylamino)-ethylamino]-9-hydroxy-2,3-dihydro-1*H*,7*H*-pyrimido-[5,6,1-*de*]acridine-1,3,7-trione dihydrobromide



C₂₃ H₂₇ N₅ O₄ · 2HBr; Mol wt: 599.3211

M.p. > 300 °C.

ACTION – Antineoplastic agent, a DNA-intercalating agent with a broad spectrum of cytotoxic activity against multidrug-resistant cell lines including ovarian carcinomas such as cisplatin-sensitive and -resistant A2780 (IC_{50} = 4.1 and 5.5 nM, respectively), cisplatin-sensitive and -resistant CH1 (IC_{50} = 7.6 and 15 nM, respectively) and SKOV-3 cell lines (IC_{50} = 42 nM), as well as against the human colon adenocarcinomas HT29 and doxorubicin-sensitive and -resistant LoVo (IC_{50} = 0.022, 0.0017 and 1.0 μ M, respectively). Other representative compounds within this series of pyrimido[5,6,1-*de*]acridine-1,3,7-triones include the following:



Compound	R1	R2=R3	X	Formula
278663	H	H	2HCl	C ₂₁ H ₂₃ N ₅ O ₃ ·2HCl
278664	NH ₂	Me	3HCl	C ₂₃ H ₂₈ N ₆ O ₃ ·3HCl

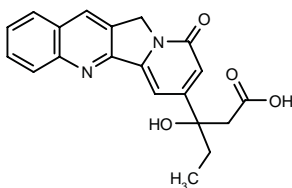
SOURCE – Roche.

REFERENCES

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278695

3-Hydroxy-3-(9-oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-7-yl)pentanoic acid



C₂₀ H₁₈ N₂ O₄; Mol wt: 350.3722

ACTION – Antineoplastic, antiparasitic and antiviral agent, an analogue of camptothecin with potent topoisomerase I- and II-inhibitory activity; it produced concentration-dependent inhibition of topoisomerase I- and II-induced relaxation of DNA with a potency higher than camptothecin and etoposide, respectively, at concentrations above 10 μ M.

SOURCE – SCRAS.

REFERENCES

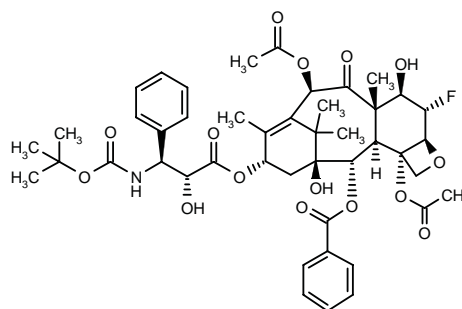
1. Bigg, D. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Novel camptothecin tetracyclic analogues, preparation, methods, applications as medicines and pharmaceutical compsns. containing them*. FR 2772763, WO 9933829.

ANTIMITOTIC DRUGS

277447

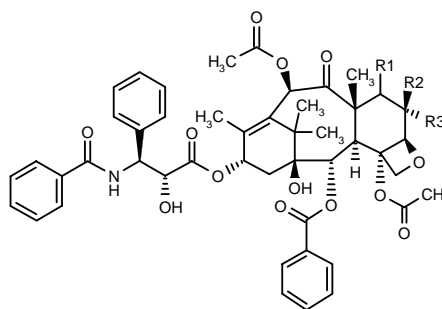
3'-*N*-*tert*-Butoxycarbonyl-3'-*N*-desbenzoyl-6 α -fluoropaclitaxel

[2*aR*,3*S*,4*R*,4*aS*,6*R*,9*S*(2'*R*,3'*S*),11*S*,12*S*,12*aR*,12*bS*]-6,12*b*-Diacetoxy-12-benzoyloxy-9-[3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionyloxy]-3-fluoro-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C₄₅ H₅₄ F N O₁₅; Mol wt: 867.9116

ACTION – Antineoplastic agent, a paclitaxel derivative with significant activity against human colon carcinoma HCT-116 cells *in vitro* (IC_{50} = 0.2 nM vs 1.53-2.73 nM for paclitaxel) and in mice bearing Madison 109 lung carcinoma, increasing survival with a T/C of 269% at a dose of 100 mg/kg i.p. Other exemplified 6-halo- or nitrate-substituted paclitaxels include the following:



Compound	R1	R2	R3	Formula
277448	OMe	H	F	C ₄₈ H ₅₂ FNO ₁₄
277449	H	Cl	H	C ₄₇ H ₅₀ ClNO ₁₃
277450	H	Br	H	C ₄₇ H ₅₀ BrNO ₁₃

SOURCE – Bristol-Myers Squibb.

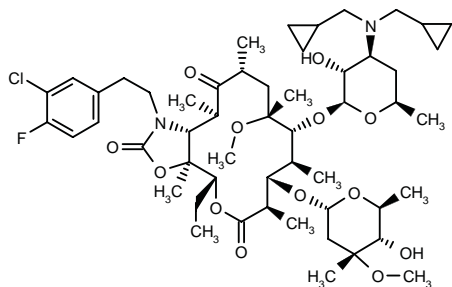
REFERENCES

1. Wittman, M.D. and Kadow, J.F. (Bristol-Myers Squibb Co.) 6-Halo- or nitrate-subst. paclitaxels. US 5912264.

HORMONAL AGENTS

277208

3',3'-*N*-Bis(cyclopropylmethyl)-3',3'-*N*-bis(demethyl)-11-[2-(3-chloro-4-fluorophenyl)ethylamino]-11-deoxy-6-*O*-methylethylerythromycin A 11-*N*,12-*O*-(cyclic carbamate)



C53 H82 Cl F N2 O13; Mol wt: 1009.6830

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist, a macrolide antibiotic that binds with high affinity to the human GnRH receptor ($K_i = 0.79$ nM) but is devoid of antibacterial activity. *In vivo*, compound significantly suppressed both luteinizing hormone (LH) levels in castrated rats (1 mg/kg by i.v. bolus) and testosterone levels in intact rats (3 mg/kg by i.v. infusion). It showed a good oral pharmacokinetic profile with a half life of 2.5 h and oral bioavailability of 25-40%. Potentially useful for the treatment of reproductive hormone-dependent disorders such as prostate and breast cancer, endometriosis, uterine leiomyoma and precocious puberty.

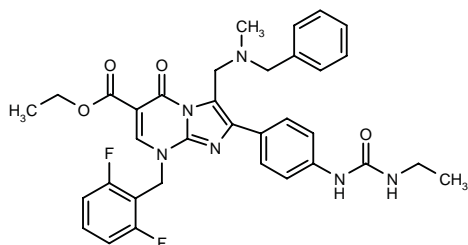
SOURCE – Abbott.

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1. Sauer, D.R. et al. (Abbott Laboratories Inc.) 3',3'-*N*-Bis-substd. macrolide LHRH antagonists. US 5972898, WO 9950276.
2. Sauer, D. et al. *The discovery, optimization, and pharmacological evaluation of novel, potent macrolide based nonpeptide antagonists of GnRH*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-224.

278696

3-(*N*-Benzyl-*N*-methylaminomethyl)-8-(2,6-difluorobenzyl)-2-[4-(3-ethylureido)phenyl]-5-oxo-5,8-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylic acid ethyl ester



C34 H34 F2 N6 O4; Mol wt: 628.6766

ACTION – Agent for the treatment of sex hormone-dependent disorders such as prostate cancer, breast cancer, uterine cancer, endometriosis, prostatic hypertrophy and precocious puberty, as well as for controlling fertility, that displays potent gonadotropin-releasing hormone (GnRH)-antagonist activity ($IC_{50} = 0.5$ nM against [^{125}I]-leuporelin binding to the human GnRH receptor expressed in CHO cells).

SOURCE – Takeda.

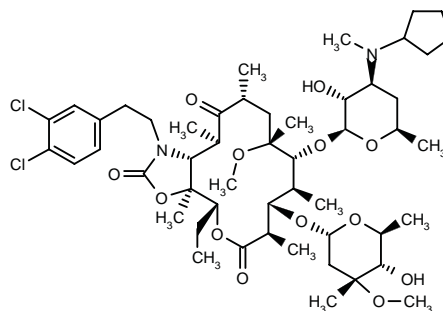
REFERENCES

1. Furuya, S. et al. (Takeda Chemical Industries, Ltd.) *Nitrogen-containing heterocyclic cpds., their production and use*. WO 9933831.

A-177775

277207

3'-*N*-Cyclopentyl-3'-*N*-demethyl-11-deoxy-11-[2-(3,4-dichlorophenyl)ethylamino]-6-*O*-methylethylerythromycin A 11-*N*,12-*O*-(cyclic carbamate)



C51 H80 Cl2 N2 O13; Mol wt: 1000.1000

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist with high affinity for human and rat GnRH receptors ($pK_i = 8.8$ and 9.1 , respectively). In functional assays, compound blocked leuprolide-induced luteinizing hormone (LH) release from rat pituitary cell cultures with a pA_2 of 9.1 . In castrated male rats, i.v. infusion at 6 and 12 mg/kg decreased plasma LH levels by 65-70% during infusion and partial suppression was maintained for 24 h; an i.p. dose of 24 mg/kg provided 70% LH suppression at 6 h. A stable chloride salt provided LH suppression comparable to i.v. infusion following i.v. bolus doses of 2, 6 and 12 mg/kg in rats. Compound showed a favorable pharmacokinetic profile in rats and dogs and was orally bioavailable (17.2% in rats). Potentially useful for the treatment of sex hormone-dependent disorders such as prostatic and breast cancer, endometriosis, uterine leiomyoma and precocious puberty.

SOURCE – Abbott.

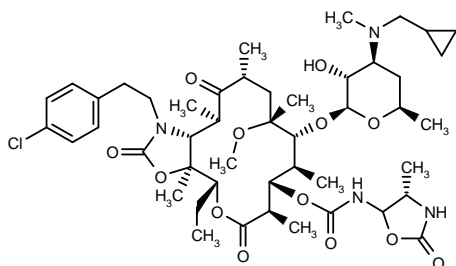
REFERENCES

1. Sauer, D.R. et al. (Abbott Laboratories Inc.) *Macrolide LHRH antagonists*. US 5955440, WO 9950275.
2. Bush, E.N. et al. *Activity and pharmacokinetics of A-177775, a non-peptide GnRH antagonist, in rats and dogs*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-225.

A-198401

277206

11-[2-(4-Chlorophenyl)ethylamino]-3'-N-(cyclopropylmethyl)-3'-N-demethyl-11-deoxy-3-O-descladinosyl-6-O-methyl-3-O-[N-[4(S)-methyl-2-oxo-5-oxazolidinyl]carbamoyl]erythromycin A 11-N,12-O-(cyclic carbamate)



C47 H71 Cl N4 O13; Mol wt: 935.5459

ACTION – Nonpeptide, orally active gonadotropin-releasing hormone (GnRH) antagonist with high affinity for human and rat GnRH receptors ($pK_i = 8.7$ and 9.2 , respectively). In functional assays, compound blocked leuprolide-induced luteinizing hormone (LH) release from rat pituitary cell cultures with a pA_2 of 8.8 . *In vivo*, it significantly suppressed LH levels in castrated rats ($ED_{50} = 5.26$ mg/kg i.v.) and testosterone levels in intact rats (24-h suppression at 10 mg/kg i.v.). Oral bioavailability in rats was approximately 20%. Compound was also able to reduce testosterone levels following i.v. dosing in intact male dogs and monkeys. Potentially useful for the treatment of sex hormone-dependent disorders such as prostatic and breast cancer, endometriosis, uterine leiomyoma and precocious puberty.

SOURCE – Abbott.

REFERENCES

1. Besecke, L.M. et al. *Pharmacological and endocrine characterization of A-198401, an orally-active GnRH antagonist, in intact and castrate male rats, dogs and cynomolgus monkeys*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-222.
2. Randolph, J.T. et al. *The design and synthesis of nonpeptide, orally active antagonist of GnRH*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-223.

CANCER IMMUNOTHERAPY

GLOBO H-KLH VACCINE

276064

Vaccine consisting of the complex carbohydrate molecule globo H hexasaccharide conjugated to keyhole limpet hemocyanin (KLH), and administered with the adjuvant QS-21

ACTION – Prostate cancer vaccine comprising globo H hexasaccharide, a ceramide-linked glycolipid expressed on the surface of cancer cells, conjugated to KLH (keyhole limpet hemocyanin) and administered with the immunological adjuvant QS-21, proven to be immunogenic, inducing specific, high-titer IgM antibodies against globo H, and safe in patients with relapsed prostate

cancer. The treatment effect (measured as a decline in the slope of the prostate-specific antigen [PSA] concentration vs. time curve) was seen to occur within 3 months after completion of vaccine therapy (5 s.c. vaccinations with 30 μ g over 26 weeks).

SOURCE – Sloan-Kettering Institute, New York, NY (US).

REFERENCES

1. Kudryashov, V. et al. *Characterization of a mouse monoclonal IgG3 antibody to the tumor-associated globo H structure produced by immunization with a synthetic glycoconjugate*. Glycoconjugate J 1998, 15(3): 243.
2. Slovin, S.F. et al. *Carbohydrate vaccines in cancer: Immunogenicity of a fully synthetic globo H hexasaccharide conjugate in man*. Proc Natl Acad Sci USA 1999, 96(10): 5710.

NBI-3001

264255

Recombinant circularly permuted IL-4-Pseudomonas exotoxin (PE) fusion toxin consisting of amino acids 38-129 of IL-4 connected by a peptide linker (GGNGG) to amino acids 1-37 and the truncated toxin PE38KDEL genetically fused to amino acid 37

IL-4(38-37)-PE38KDEL

ACTION – Antineoplastic agent, a recombinant chimeric cytotoxin comprised of a circularly permuted human IL-4 fused to the translocation and enzymatic domains of *Pseudomonas* exotoxin; it is able to bind with high affinity to IL-4 receptors (IL-4R), and it showed high cytotoxicity against IL-4R-bearing glioblastoma cell lines. In nude mice, compound eradicated both glioblastoma U-251 and AIDS-associated Kaposi's sarcoma xenografts and prevented tumor-associated symptoms without any evidence of toxicity. The IL-4 toxin is now undergoing phase I/II clinical trials for the treatment of human glioblastoma.

SOURCES – National Institutes of Health, Bethesda, MD (US); Neurocrine Biosciences.

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1. Husain, S.R. et al. *Antitumor activity of interleukin-4 toxin in nude mice implanted with AIDS-associated Kaposi's sarcoma tumor*. 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 22279.
2. Husain, S.R. et al. *Complete regression of established human glioblastoma tumor xenograft by interleukin-4 toxin therapy*. Cancer Res 1998, 58(16): 3649.
3. Husain, S.R. et al. *Interleukin-4 receptor expression on AIDS-associated Kaposi's sarcoma cells and their targeting by a chimeric protein comprised of circularly permuted interleukin-4 and Pseudomonas exotoxin*. Mol Med 1997, 3(5): 327.
4. Husain, S.R. et al. *Interleukin-4 receptor-directed cytotoxic therapy of AIDS-associated Kaposi's sarcoma tumors in xenograft model*. Nat Med 1999, 5(7): 817.
5. Kreitman, R.J. et al. *A circularly permuted recombinant interleukin 4 toxin with increased activity*. Proc Natl Acad Sci USA 1994, 91(15): 6889.
6. Kreitman, R.J. et al. *Increased antitumor activity of a circularly permuted interleukin 4-toxin in mice with interleukin 4 receptor-bearing human carcinoma*. Cancer Res 1995, 55(15): 3357.
7. Mesri, E.A. *Targeting AIDS-Kaposi's sarcoma*. Nat Med 1999, 5(7): 738.
8. Puri, R.K. et al. *An improved circularly permuted interleukin 4-toxin is highly cytotoxic to human renal cell carcinoma cells. Introduction of gamma chain in RCC cells does not improve sensitivity*. Cell Immunol 1996, 171(1): 80.
9. Puri, R.K. et al. *Preclinical development of a recombinant toxin containing circularly permuted interleukin 4 and truncated Pseudomonas exotoxin for therapy of malignant astrocytoma*. Cancer Res 1996, 56(24): 5631.

10. *Clinical development - Malignant brain tumor (NBI-3001)*. Neurocrine Biosciences Product Pipeline 1999, Aug 2.

11. *Data from phase I/II study of NBI-3001 presented at German Society of Neurosurgery*. DailyDrugNews.com (Daily Essentials) 1999, June 11.

12. *IL-4 fusion toxin effective in preclinical Kaposi's sarcoma models*. DailyDrugNews.com (Daily Essentials) 1999, July 2.

13. *Neurocrine Biosciences advances development of NBI-3001*. DailyDrugNews.com (Daily Essentials) 1998, Nov 30.

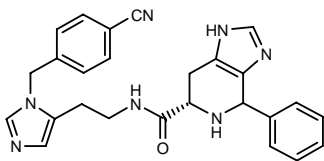
14. *Neurocrine Biosciences initiates clinical-stage development of IL-4 fusion toxin*. DailyDrugNews.com (Daily Essentials) 1998, May 19.

15. *Neurocrine Biosciences: Q3 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, Nov 19.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

277404

N-[2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]ethyl]-4-phenyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6(*S*)-carboxamide



C₂₆ H₂₅ N₇ O; Mol wt: 451.5315

ACTION – Peptidomimetic protein farnesyltransferase inhibitor potentially useful in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease.

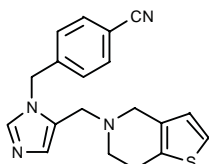
SOURCE – Merck & Co.

REFERENCES

1. Ciccarone, T.M. and deSolms, S.J. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9927928.

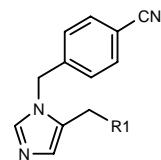
277405

4-[5-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-5-ylmethyl)-1*H*-imidazol-1-ylmethyl]benzonitrile



C₁₉ H₁₈ N₄ S; Mol wt: 334.4452

ACTION – Peptidomimetic protein farnesyltransferase inhibitor potentially useful in the treatment or prevention of cancer, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease. Other preferred compounds are:



Compound	R1	Formula
277406	2-Br-4,5,6,7-tetrahydrothieno-[2,3- <i>c</i>]pyridin-5-yl	C ₁₉ H ₁₇ BrN ₄ S
277407	2-Ph-4,5,6,7-tetrahydrothieno-[2,3- <i>c</i>]pyridin-5-yl	C ₂₅ H ₂₂ N ₄ S
277408	5H-imidazo[4,5- <i>b</i>]pyridin-5-yl	C ₁₈ H ₁₄ N ₆
277409	4H-imidazo[4,5- <i>b</i>]pyridin-4-yl	C ₁₈ H ₁₄ N ₆

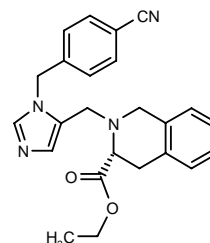
SOURCE – Merck & Co.

REFERENCES

1. Halczenko, W. and Stump, C.A. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9927929.

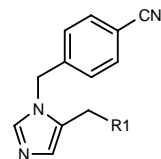
277551

2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]-1,2,3,4-tetrahydroisoquinoline-3(*R*)-carboxylic acid ethyl ester



C₂₄ H₂₄ N₄ O₂; Mol wt: 400.4796

ACTION – Peptidomimetic compound with inhibitory activity against protein farnesyltransferase and therefore expected to be of use in the treatment or prevention of cancer, benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease. Other specifically claimed compounds include the following:



Compound	R1	Formula
277552	7-Ph-1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₇ H ₂₄ N ₄
277553	3(<i>S</i>)-(3-Cl-PhCH ₂ NHCO)-1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₉ H ₂₆ ClN ₅ O
277554	7-Br-1-Bu-1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₅ H ₂₇ BrN ₄
277555	1-indolyl	C ₂₀ H ₁₆ N ₄
277556	2,3-dihydro-1-indolyl	C ₂₀ H ₁₈ N ₄
277557	1-indazolyl	C ₁₉ H ₁₅ N ₅
277558	1,2,3,4-tetrahydro-1-quinolinyl	C ₂₁ H ₂₀ N ₄
277559	1-benzimidazolyl	C ₁₉ H ₁₅ N ₅
277560	1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₁ H ₂₀ N ₄
277561	6,7-(MeO)2-1,2,3,4-tetrahydro-2-isoquinolinyl	C ₂₃ H ₂₄ N ₄ O ₂
277562	3-(PhCH ₂)-2-imino-1-benzimidazolyl	C ₂₆ H ₂₂ N ₆

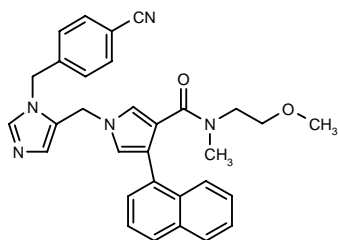
SOURCE – Merck & Co.

REFERENCES

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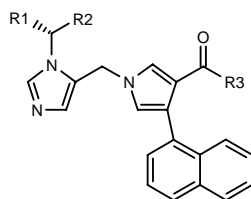
277570

1-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]-*N*-(2-methoxyethyl)-*N*-methyl-4-(1-naphthyl)-1*H*-pyrrole-3-carboxamide



C31 H29 N5 O2; Mol wt: 503.6031

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase and the farnesylation of Ras. Compound exhibited IC₅₀ values of 0.0006 and 0.0015 μM, respectively, when tested against recombinant farnesyltransferase using H- and K-Ras as the substrate. In addition, it was also highly active in H-ras-transformed Rat2 cells (IC₅₀ = 0.008 μM). Within this series of imidazole derivatives, the following are also included:



Compound	R1	R2	R3	Formula
277571	Me	Ph	4-Me-1-Piz	C ₃₂ H ₃₃ N ₅ O
277572	Ph	Me	4-Me-1-Piz	C ₃₂ H ₃₃ N ₅ O
277573	H	2-Naph-CH2	4-Me-1-Piz	C ₃₆ H ₃₅ N ₅ O
277574	H	4-OH-PhCH2	4-Me-1-Piz	C ₃₂ H ₃₃ N ₅ O ₂
277575	H	4-Br-Ph	N(Me)CH2CH2OMe	C ₃₀ H ₂₅ BrN ₄ O ₂
277576	H	4-Br-Ph	4-morpholinyl	C ₃₀ H ₂₇ BrN ₄ O ₂
277577	H	4-Br-Ph	4-Me-1-Piz	C ₃₁ H ₃₀ BrN ₅ O
277578	H	4-Cl-Ph	4-Me-1-Piz	C ₃₁ H ₃₀ ClN ₅ O
277579	H	4-F-Ph	N(Me)CH2CH2OMe	C ₃₀ H ₂₉ FN ₄ O ₂
277580	H	4-F-Ph	4-Me-1-Piz	C ₃₁ H ₃₀ FN ₅ O

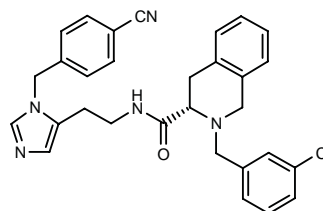
SOURCE – LG Chem.

REFERENCES

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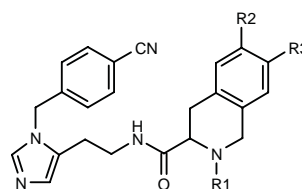
277629

2-(3-Chlorobenzyl)-*N*-[2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]ethyl]-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxamide

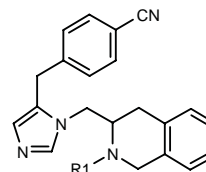


C30 H28 Cl N5 O; Mol wt: 510.0382

ACTION – Peptidomimetic compound with the ability to inhibit protein farnesyltransferase, potentially useful for treating cancer, blindness related to retinal vascularization, infections caused by hepatitis delta and related viruses, benign proliferative disorders and polycystic kidney disease. Other specifically claimed compounds are:



Compound	R1	R2	R3	Isomer	Formula
277630	3-Cl-PhSO2	H	H	S	C ₂₈ H ₂₆ ClN ₅ O ₃ S
277632	Bu	H	H	S	C ₂₇ H ₃₁ N ₅ O
277633	3-Pyr-CH2	H	H	S	C ₂₉ H ₂₈ N ₆ O
277634	3-MeO-PhCH2	H	H	R	C ₃₁ H ₃₁ N ₅ O ₂
277635	3-Cl-PhCH2	OMe	H	S	C ₃₁ H ₃₀ ClN ₅ O ₂
277640	5-Cl-2-oxo-1,2-dihydro-1-Pyr-CH2CH2	H	OMe	S	C ₃₂ H ₃₅ ClN ₆ O ₃



Compound	R1	Isomer	Formula
277636	5-Cl-2-oxo-1,2-dihydro-1-Pyr-CH2CO	R	C ₂₈ H ₂₄ ClN ₅ O ₂
277637	CH2CH2SO2Me	S	C ₂₄ H ₂₆ N ₄ O ₂ S
277638	3-MeO-PhCO	S	C ₂₉ H ₂₆ N ₄ O ₂

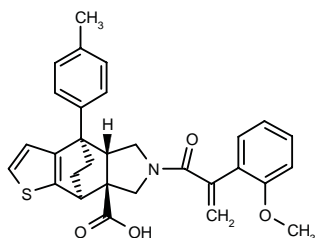
SOURCE – Merck & Co.

REFERENCES

1. Ciccarone, T.M. and deSolms, S.J. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. US 5932590, WO 9928314.

278697

(3a*RS*,4*SR*,8*SR*,8a*RS*)-6-[2-(2-Methoxyphenyl)-2-propenoyl]-4-(4-methylphenyl)-4a,5,6,7,8-hexahydro-4*H*-4,8-ethanothieno[2,3-*f*]isoindole-7a-carboxylic acid



C30 H29 N O4 S; Mol wt: 499.6281

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras.

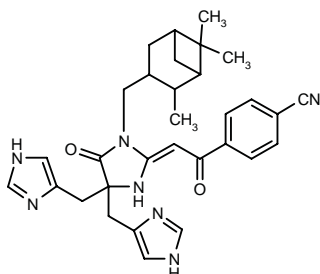
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Dereu, N. et al. (Rhône-Poulenc Rorer SA) *Novel farnesyl transferase inhibitors, preparation, pharmaceutical compns. containing them and use for preparing medicines*. FR 2772764, WO 9933834.

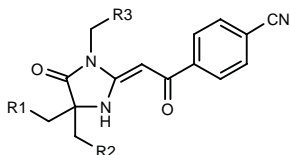
278783

(–)-4-[2-[4,4-Bis(1*H*-imidazol-4-ylmethyl)-5-oxo-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-ylmethyl)imidazolidin-2-ylidene]acetyl]benzonitrile

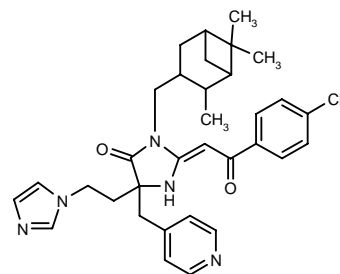


C31 H35 N7 O2; Mol wt: 537.6645

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of imidazolidin-4-one derivatives include the following:



Compound	R1=R2	R3	Formula
278784	1-Me-5-imidazolyl	2,6,6-(Me)3-bicyclo[3.1.1]hept-3-yl	C ₃₃ H ₃₉ N ₇ O ₂
278785	4-imidazolyl	2,6,6-(Me)3-bicyclo[3.1.1]hept-3-yl	C ₃₁ H ₃₅ N ₇ O ₂
278787	1-Me-5-imidazolyl	1-adamantyl	C ₃₃ H ₃₇ N ₇ O ₂



278786: C34 H38 N6 O2

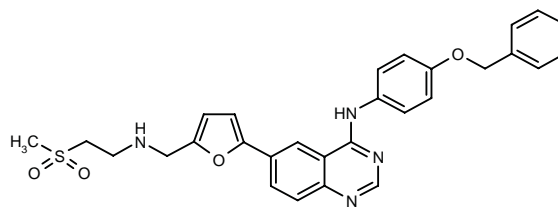
SOURCE – Pfizer.

REFERENCES

1. Lyssikatos, J.P. and Yang, B.V. (Pfizer Products Inc.) *Imidazolidin-4-one derivs. useful as anticancer agents*. CA 2257016, EP 928788, JP 99236333.

278855

N-[5-[4-[4-(Benzyloxy)phenylamino]quinazolin-6-yl]furan-2-ylmethyl]-*N*-[2-(methylsulfonyl)ethyl]amine



C29 H28 N4 O4 S; Mol wt: 528.6302

ACTION – Potent inhibitor of protein tyrosine kinases, particularly c-erbB2 and epidermal growth factor (EGF) receptor tyrosine kinase, as demonstrated by IC₅₀ values < 0.10 μM in a substrate phosphorylation assay. Antiproliferative activity was demonstrated *in vitro* in erbB2-transfected human mammary epithelial HB4a, human breast carcinoma BT474, human head and neck carcinoma HN5 and human gastric tumor N87 cells by IC₅₀ values < 5 μM. A representative compound from a series of bicyclic heteroaryl derivatives.

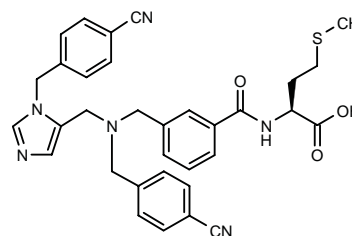
SOURCE – Glaxo Wellcome.

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1. Carter, M.C. et al. (Glaxo Group Ltd.) *Bicyclic heteroaromatic cpds. as protein tyrosine kinase inhibitors*. WO 9935146.

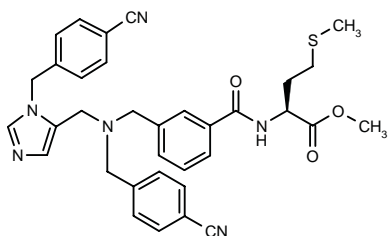
278860

N-[3-[*N*-(4-Cyanobenzyl)-*N*-[1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]aminomethyl]benzoyl]-L-methionine



C33 H32 N6 O3 S; Mol wt: 592.7208

ACTION – Antineoplastic agent, a potent protein farnesyltransferase inhibitor ($IC_{50} = 0.41$ nM). The corresponding **methyl ester prodrug** was a highly selective and potent inhibitor of *ras*-transformed cell growth and Ras processing in cell culture:



278861: C₃₄ H₃₄ N₆ O₃ S

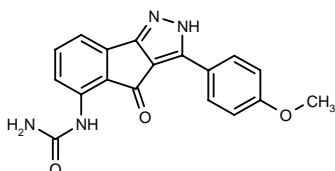
SOURCE – Merck & Co.

REFERENCES

1. Ciccarone, T.M. et al. *Non-thiol 3-aminomethylbenzamide inhibitor of farnesyl-protein transferase*. Bioorg Med Chem Lett 1999, 9(14): 1991.

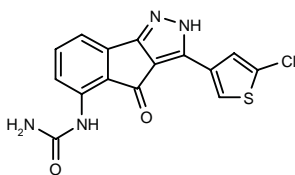
279685

N-[3-(4-Methoxyphenyl)-4-oxo-2,4-dihydroindeno[1,2-*c*]pyrazol-5-yl]urea



C₁₈ H₁₄ N₄ O₃; Mol wt: 334.3336

ACTION – Potential antineoplastic agent, an inhibitor of cyclin-dependent kinases. Another specifically claimed indenopyrazole is:



279686: C₁₅ H₉ Cl N₄ O₂ S

SOURCE – DuPont Pharmaceuticals.

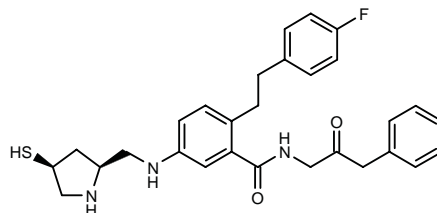
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1. Nugiel, D.A. et al. (Du Pont Pharmaceuticals Co.) *5-Aminoindeno(1,2-*c*)pyrazol-4-ones as anti-cancer and anti-proliferative agents*. WO 9954308.

2. Seitz, S.P. et al. *Characterization of indenopyrazoles as inhibitors of cyclin-dependent kinases*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MED1 316.

279947

2-[2-(4-Fluorophenyl)ethyl]-*N*-(2-oxo-3-phenylpropyl)-5-[4(*S*)-sulfanylpiperidin-2(*S*)-ylmethylamino]benzamide



C₂₉ H₃₂ F N₃ O₂ S; Mol wt: 505.6548

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} about 0.1 μ M) proven to inhibit the proliferation of human pancreatic carcinoma MIA PaCa-2 cells ($IC_{50} = 0.3$ -1.0 μ M).

SOURCE – AstraZeneca.

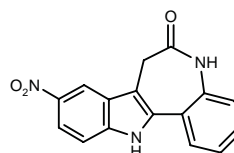
REFERENCES

1. Drake, D.J. and Wardleworth, J.M. (Zeneca Ltd.) *Farnesyl transferase inhibitors*. WO 9941235.

ALSTERPAULLONE

277566

9-Nitro-7,12-dihydroindolo[3,2-*d*]-1-benzazepin-6(*5H*)-one



C₁₆ H₁₁ N₃ O₃; Mol wt: 293.2809

Yellow crystals, m.p. > 300 °C.

ACTION – Antineoplastic agent, an inhibitor of cyclin-dependent kinases (CDK) with selectivity for CDK1/cyclin B ($IC_{50} = 35$ nM); it is at least 10-fold more potent than kenpaullone, flavopiridol and roscovitine. Compound showed activity in the NCI anticancer drug screen of 60 human tumor cell lines, in particular against human colon cancer HCT-116.

SOURCES – CNRS; Universität Hamburg, Hamburg (DE); National Cancer Institute, Bethesda, MD (US).

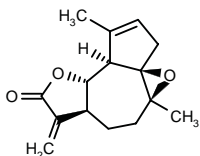
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1. Schultz, C. et al. *Paullones, a series of cyclin-dependent kinase inhibitors: Synthesis, evaluation of CDK1/cyclin B inhibition, and in vitro antitumor activity*. J Med Chem 1999, 42(15): 2909.

ARGLABIN

279342

(3a*R*,4a*S*,6a*S*,9a*R*,9b*R*)-1,4a-Dimethyl-7-methylene-4a,5,6,6a,7,8,9a,9b-octahydro-3*H*-oxireno[8,8a]-azuleno[4,5-*b*]furan-8-one



C15 H18 O3; Mol wt: 246.3042

ACTION – Antineoplastic agent, a sesquiterpene lactone originally isolated from wormwood (*Artemisia*) that acts as a selective inhibitor of protein farnesyltransferase (IC_{50} = 250 μ M) and inhibits Ras processing in H-*ras*- and K-*ras*-transformed cells (IC_{50} = 2.5 and 5 μ g/ml, respectively). Compound inhibited cell proliferation in a variety of tumor types (including neuroblastoma cells; IC_{90} = 10 μ g/ml) with IC_{90} values ranging from 0.85 to 3.75 μ g/ml. Compound also induced significant macrophage cytotoxic activity and stimulated mitochondrial metabolism, and stimulated the production of IL-1, TNF- α and IL-2, as well as phagocytosis, in J774.1 cells. The compound is reported to be effective against Lewis lung cancer, breast adenocarcinoma Ca-755, liver carcinoma PC-1, lymphoid leukemia P388 and sarcoma 45, among others, in laboratory animals and to have low toxicity. Promising results and few side effects have been reported in clinical studies in cancer patients in Russia, where the drug is approved for use.

SOURCES – NuOncology Labs; Institute of Phytochemistry, Karaganda (KZ).

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- Adekenov, S.M. *Method and device for production of lyophilized hydrochloride-1beta,10beta-epoxy-13-dimethylamino-guaia-3(4)-en-6,12-olide.* WO 9828303.
- Udagawa, T. et al. (Children's Medical Center Corp.) *Cytochalasin and isoindolinone derivs. as inhibitors of angiogenesis.* WO 9841205.
- Adekenov, S.M. et al. *Arglabin - A new sesquiterpene lactone from Artemisia glabella.* Khim Prii Soedin 1982, 5655.
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- Appendino, G. et al. *The stereochemistry of arglabin, a cytotoxic guaianolide from Artemisia myriantha.* Fitoterapia 1991, 62(3): 275.
- Bottex-Gauthier, C. et al. *In vitro biological activities of arglabin, a sesquiterpene lactone from the Chinese herb Artemisia myriantha Wall. (Asteraceae).* Biotechnol Ther 1993, 4(1-2): 77.
- Kagarlitskii, A.D. and Adekenov, S.M. *New sesquiterpene lactones from plants of central Kazakhstan.* Izv Akad Nauk Kaz SSR. Ser Khim 1984, 437.
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- Shaikenov, T.E. et al. *Arglabin inhibits farnesylation of Ras protein and cell proliferation.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2474.
- Shaikenov, T.E. et al. *Arglabin as a novel inhibitor of the farnesylation of Ras proteins.* Dokl Ministerstvo Nauki - Akad Nauk Resp Kazakhstan 1998, 564.

13. Shaikenov, T.E. et al. *Selective effect of arglabin on transformed vs. normal cells in vitro.* Vestn Ministerstva Nauki - Akad Nauk Resp Kazakhstan 1996, 655.

14. Shaikenov, T.E. et al. *The blocking of tumor's cell proliferation by defarnesylation of proteins.* Dokl Ministerstvo Nauki - Akad Nauk Resp Kazakhstan 1997, 369.

15. *Antitumor candidate originating in Kazakhstan slated for development in U.S. and other countries.* DailyDrugNews.com (Daily Essentials) 1999, Jan 18.

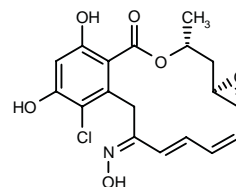
16. *NuOncology Labs awarded U.S. patent for anticancer compounds.* DailyDrugNews.com (Daily Essentials) 1999, Aug 2.

KF-25706*

245785

13-Chloro-5(*R*),6(*S*)-epoxy-14,16-dihydroxy-11-(hydroxyimino)-3(*R*)-methyl-3,4,5,6,11,12-hexahydro-1*H*-2-benzoxacyclotetradecin-1-one

UCS1006-S15



C18 H18 Cl N O6; Mol wt: 379.7942

ACTION – Antineoplastic agent, a derivative of the macrocyclic antifungal antibiotic radicicol that inhibits multiple signal transduction pathways. Like radicicol, compound was able to inhibit both tyrosine kinase activity in *v-src*-transformed rat fibroblast cells (IC_{50} = 120 nM) and Erk phosphorylation in K-*ras*-transformed rat epithelial cells (IC_{50} = 100 nM). It exhibited antiproliferative activity against various human tumor cell lines such as breast carcinoma MCF-7 and SK-BR-3 (IC_{50} = 77 and 29 nM, respectively), colon carcinoma DLD-1 and HCT-116 (IC_{50} = 40 and 110 nM, respectively), lung carcinoma A549 (IC_{50} = 150 nM), prostate carcinoma PC-3 and DU-145 (51 and 35 nM, respectively), and epidermoid carcinoma A431 (IC_{50} = 210 nM). Compound (100 mg/kg i.v. b.i.d. for 5 days) was also shown to possess antitumor activity against both estrogen receptor-negative MX-1 and estrogen receptor-positive MCF-7 breast carcinomas, colon carcinoma DLD-1 and epidermoid carcinoma A431 xenografts in mice, without liver or renal toxicity. Its antitumor activity is suggested to be mediated, at least in part, by binding to Hsp90 family chaperone proteins and destabilization of Hsp90-associated signaling molecules.

SOURCES – Kyowa Hakko; National Cancer Institute, Bethesda, MD (US).

REFERENCES

- Agatsuma, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Radical derivs.* EP 823429, WO 9633989.
- Akinaga, S. et al. *KF25706 (UCS1006-S15): A novel derivative of radicicol inhibiting multiple signal transduction pathways with in vivo antitumor activity in breast carcinoma xenograft models.* Proc Amer Assoc Cancer Res 1998, 39: Abst 2186.
- Soga, S. et al. *KF25706, a novel oxime derivative of radicicol, exhibits in vivo antitumor activity via selective depletion of Hsp90 binding signaling molecules.* Cancer Res 1999, 59(12): 2931.

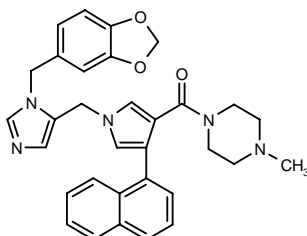
*Identified compound **245785** (see **244392**) Drug Data Rep 1997, 019(04): 0363.

LB-42908

279623

1-[1-[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-imidazol-5-ylmethyl]-4-(1-naphthyl)-1*H*-pyrrol-3-yl]-1-(4-methyl-1-piperazinyl)methanone

1-[1-[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-imidazol-5-ylmethyl]-4-(1-naphthyl)-1*H*-pyrrol-3-ylcarbonyl]-4-methylpiperazine



C32 H31 N5 O3; Mol wt: 533.6289

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor (IC_{50} = 1.7, 1.8 and 3.5 nM against H-*ras*, N-*ras* and K-*ras*, respectively) with excellent selectivity over protein geranylgeranyltransferase-I (IC_{50} = 16,000 nM). Compound potently inhibited the proliferation of various human tumor cells including colon HT29 and HCT116 (GI_{50} = 4.5 and 17.6 nM, respectively), bladder EJ and T24 (GI_{50} = 20 and 0.45 nM, respectively) and lung A549 (GI_{50} = 1.2 nM), as well as of *ras*-transformed Rat2/H-*ras* and Rat2/K-*ras*4B cell lines (GI_{50} = 3.0 and 112 nM, respectively). In nude mice, compound given orally strongly inhibited the growth of human colon carcinoma HCT116 (78.4% at 40 mg/kg b.i.d. for 30 days) and human bladder carcinoma EJ (98.7% at 40 mg/kg b.i.d. for 25 days) xenografts. It exhibited a favorable pharmacokinetic profile with excellent oral bioavailability in rats, dogs and monkeys (61, 71 and 91%, respectively).

SOURCE – LG Chem.

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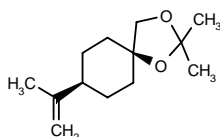
2. Lee, H. et al. *Synthesis and structure-activity relationships of 1-(1(3*H*-imidazole-5(4*H*)-yl)-methylpyrroles as farnesyl protein transferase inhibitors (FTPI)*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 210.

3. *Pyrrole-based orally active farnesyl protein transferase inhibitor-LB42908*. LG Chem Product Fact Sheet 1999.

XR-3054

278816

cis-8-Isopropenyl-2,2-dimethyl-1,3-dioxaspiro[4.5]decane



C13 H22 O2; Mol wt: 210.3148

Colorless oil.

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor (IC_{50} = 50 μ M for inhibition of farnesylation of CAAX recognition peptides) that is able to reduce the anchorage-independent growth of V12 H-*ras*-transformed NIH3T3 cells with an IC_{50} of 30 μ M, as well as the phosphorylation of p42 mitogen-activated protein (MAP) kinase in both parental NIH3T3 cells and V12 H-*ras*-transformed NIH3T3 cells. Compound inhibited the proliferation of prostatic carcinoma LnCAP and PC3 cells (IC_{50} = 12.4 and 12.2 μ M, respectively) and colon carcinoma SW480 and HT1080 cells (IC_{50} = 21.4 and 8.8 μ M, respectively) but was inactive against a panel of breast carcinoma cell lines (IC_{50} > 100 μ M).

SOURCE – Xenova.

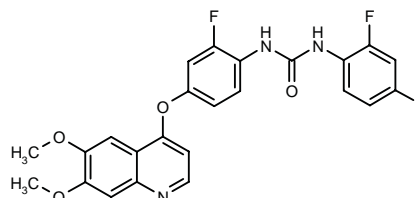
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ANGIOGENESIS INHIBITORS

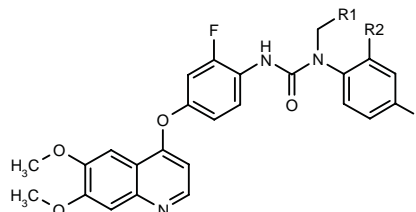
278483

N-(2,4-Difluorophenyl)-*N'*-[4-(6,7-dimethoxyquinolin-4-yloxy)-2-fluorophenyl]urea



C24 H18 F3 N3 O4; Mol wt: 469.4172

ACTION – Agent for the treatment of cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis and atherosclerosis, proven to inhibit tumor blood flow and tumor growth in nude mice bearing human glioma GL07 tumors (84% inhibition at 10 mg/kg/day p.o. x 9 days). It was also shown to be active in models of collagen-induced arthritis and delayed-type hypersensitivity in mice following oral administration. Other compounds within this series of quinoline derivatives include the following:



Compound	R1	R2	Formula
278484	H	F	C ₂₈ H ₂₀ F ₃ N ₃ O ₄
278485	Me	H	C ₂₈ H ₂₃ F ₂ N ₃ O ₄

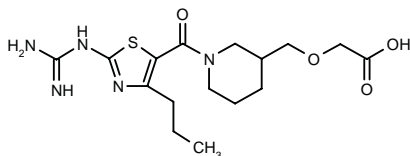
SOURCE – Kirin Brewery.

REFERENCES

1. Kubo, K. et al. (Kirin Brewery Co., Ltd.) *Quinoline derivs. and medicinal compsns. containing them*. JP 99158149.

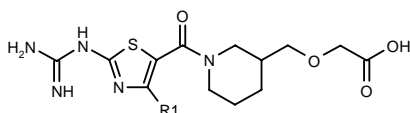
278702

2-[1-(2-Guanidino-4-propylthiazol-5-ylcarbonyl)-3-piperidinylmethoxy]acetic acid



C16 H25 N5 O4 S; Mol wt: 383.4705

ACTION – An inhibitor of the binding of adhesive proteins such as fibrinogen, vitronectin, fibronectin, von Willebrand factor, thrombospondin and osteopontin to the vitronectin receptor ($\alpha_v\beta_3$) and related integrins such as $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ on the surface of various types of cells, thus influencing cell–cell and cell–matrix interactions. *In vitro*, compound exhibited an IC_{50} value of 0.018 μ M for inhibition of the binding of fibrinogen to the human $\alpha_v\beta_3$ receptor. Potentially useful for the treatment or prevention of cancer, osteoporosis, Paget's disease, diabetic retinopathy, macular degeneration, restenosis, psoriasis, arthritis, fibrosis, renal failure and bacterial, fungal and viral infections. Other specifically claimed compounds from this series of thiazole derivatives include the following:



Compound	R1	Isomer	Formula
278703	Me	R	C ₁₄ H ₂₁ N ₅ O ₄ S
278704	cyclopentyl	racemic	C ₁₈ H ₂₇ N ₅ O ₄ S
278705	Me	racemic	C ₁₄ H ₂₁ N ₅ O ₄ S
278706	Ph	racemic	C ₁₉ H ₂₃ N ₅ O ₄ S
278707	t-Bu	racemic	C ₁₇ H ₂₇ N ₅ O ₄ S

SOURCE – Roche.

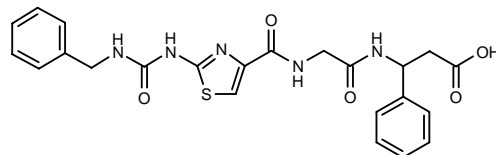
REFERENCES

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278708

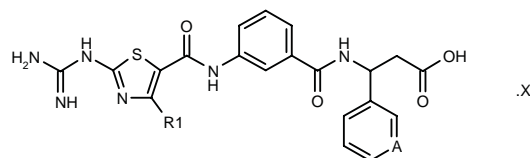
(±)-N-[2-[2-(3-Benzylureido)thiazol-4-ylcarboxamido]acetyl]-3-phenyl-β-alanine

(±)-3-[2-[2-(3-Benzylureido)thiazol-4-ylcarboxamido]acetamido]-3-phenylpropionic acid

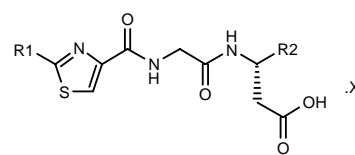


C23 H23 N5 O5 S; Mol wt: 481.5307

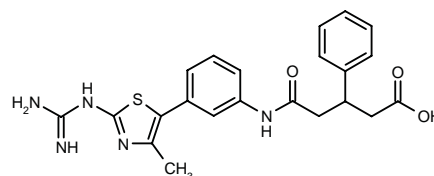
ACTION – An inhibitor of the binding of adhesive proteins such as fibrinogen, vitronectin, fibronectin, von Willebrand factor, thrombospondin and osteopontin to the vitronectin receptor ($\alpha_v\beta_3$) and related integrins such as $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ on the surface of various types of cells, thus influencing cell–cell and cell–matrix interactions. Potentially useful for the treatment or prevention of cancer, osteoporosis, Paget's disease, diabetic retinopathy, macular degeneration, restenosis, psoriasis, arthritis, fibrosis, renal failure and bacterial, fungal and viral infections. Other specifically claimed compounds from this series of thiazole derivatives include the following:



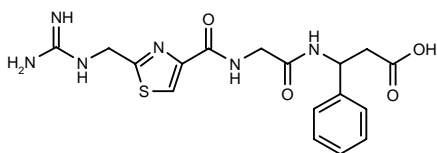
Compound	R1	A	X	Formula
278711	Me	CH	HCl	C ₂₂ H ₂₂ N ₆ O ₄ S .HCl
278712	t-Bu	N		C ₂₄ H ₂₇ N ₇ O ₄ S



Compound	R1	R2	X	Formula
278713	NHC(=NH)NH2	-CO-L-Val-OH	HCl	C ₁₆ H ₂₃ N ₇ O ₇ S .HCl
278714	NHCONHCH2Ph	CONHCH2Ph	CF3CO2H	C ₂₅ H ₂₆ N ₆ O ₆ S .C ₂ HF ₃ O ₂



278709: C22 H23 N5 O3 S



278710: C₁₇ H₂₀ N₆ O₄ S

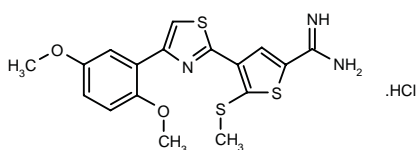
SOURCE – Roche.

REFERENCES

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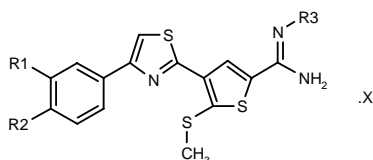
279833

4-[4-(2,5-Dimethoxyphenyl)thiazol-2-yl]-5-(methylsulfonyl)thiophene-2-carboxamide hydrochloride



C₁₇ H₁₇ N₃ O₂ S₃ . HCl; Mol wt: 427.9992

ACTION – Potent inhibitor of trypsin-like serine proteases with selective activity against urokinase (uPA or urinary-type plasminogen activator; $K_i < 2.5 \mu\text{M}$ using human kidney urokinase). As such, it is considered to be potentially useful for the treatment of angiogenesis, arthritis, inflammatory disorders, restenosis, tumor invasion and metastasis, osteoporosis and retinopathy. Other representative compounds from this series of heteroaryl amidines, methylamidines and guanidines are:



Compound	R1	R2	R3	X	Formula
279834	OMe	H	H	HCl	C ₁₆ H ₁₅ N ₃ O ₃ .HCl
279835	H	NO ₂	H	HCl	C ₁₅ H ₁₂ N ₄ O ₂ S ₃ .HCl
279836	H	H	CN		C ₁₆ H ₁₂ N ₄ S ₃
279837	4-morpholinyl- -COCH ₂ O	H	H	CF ₃ CO ₂ H	C ₂₁ H ₂₂ N ₄ O ₅ S ₃ .C ₂ HF ₃ O ₂
279838	OCH ₂ CO ₂ H	H	H		C ₁₇ H ₁₅ N ₃ O ₃ S ₃

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

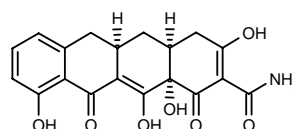
1. Illig, C.R. et al. (3-Dimensional Pharmaceuticals, Inc.) *Heteroaryl amidines, methylamidines and guanidines as protease inhibitors, in particular as urokinase inhibitors.* WO 9940088.

METASTAT™

271939

(4a*S*,5a*R*,12a*S*)-3,10,12,12a-Tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydronaphthacene-2-carboxamide

CMT-3
COL-3
NSC-683551



C₁₉ H₁₇ N O₇; Mol wt: 371.3433

ACTION – Orally bioavailable matrix metalloproteinase (MMP) inhibitor particularly active against collagenase 3 (MMP-13; IC₅₀ = 0.3 $\mu\text{g/ml}$), a modified tetracycline that is able to block malignant tumor cell invasion into normal lung tissue in rat and mouse models of metastasis. Compound is currently undergoing phase I clinical trials in patients with a range of solid tumors including breast, lung, colon, prostate and brain cancer refractory to standard therapy.

SOURCES – CollaGenex; National Cancer Institute, Bethesda, MD (US).

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- Amin, A.R. et al. (State University of New York, Albany) *Method of using tetracycline cpds. for inhibition of nitric oxide production.* WO 9808480.
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- Golub, L.M. et al. (State University of New York, Albany) *Compsn. comprising flurbiprofen and effectively non-antibacterial tetracycline to reduce bone loss.* CA 2031368, US 5321017.
- Golub, L.M. et al. (State University of New York, Albany) *Tetracyclines including non-antimicrobial chemically-modified tetracyclines inhibit excessive collagen crosslinking during diabetes.* EP 599397, JP 94256280, US 5532227.
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- McNamara, T.F. et al. (State University of New York, Albany) *Non-antibacterial tetracycline compsns. possessing antiplaque properties.* CA 2094874.
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19. Rodman, L. et al. *Preclinical dose range-finding studies of COL-3 (NSC-683551) in rats and monkeys*. *Proc Amer Assoc Cancer Res* 1997, 38: Abst 4021.

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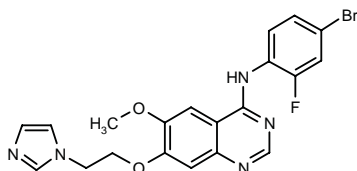
22. *Initial findings reported for CollaGenex's anticancer compound*. *DailyDrugNews.com* (Daily Essentials) 1999, Feb 17.

23. *Spotlight on angiogenesis inhibitors in clinical testing*. *DailyDrugNews.com* (Daily Essentials) 1998, Sept 22.

ZD-4190

258503

N-(4-Bromo-2-fluorophenyl)-7-[2-(1*H*-imidazol-1-yl)ethoxy]-6-methoxyquinazoline-4-amine



C20 H17 Br F N5 O2; Mol wt: 458.2893

ACTION – Antineoplastic agent, an ATP-competitive vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor able to prevent the VEGF-stimulated proliferation of human umbilical vein endothelial cells (HUVEC) *in vitro*. Compound given orally significantly inhibited the growth and reduced the vascular permeability of a number of human tumor xenografts such as breast, colon, lung, ovarian and prostate tumors. It significantly inhibited VEGF-mediated hypotension in rats but did not affect hypotension induced by basic fibroblast growth factor (bFGF) or acetylcholine.

SOURCE – AstraZeneca.

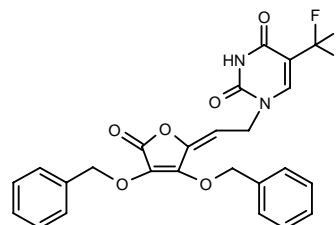
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3. Ogilvie, D.J. et al. *ZD4190: An orally administered inhibitor of VEGF signalling with pan-xenograft anti-tumor activity*. *Proc Amer Assoc Cancer Res* 1999, 40: Abst 458.
4. Wedge, S.R. et al. *Effect of the VEGF receptor tyrosine kinase inhibitor ZD4190 on vascular endothelial permeability*. *Proc Amer Assoc Cancer Res* 1999, 40: Abst 2741.
5. *87 development projects under way at Zeneca*. *DailyDrugNews.com* (Daily Essentials) 1997, Dec 16.

OTHER ONCOLYTIC DRUGS

278675

1-[2-[3,4-Bis(benzyloxy)-5-oxofuran-2-ylidene]ethyl]-5-trifluoromethyl-1,3-dihydropyrimidine-2,4-dione



C25 H19 F3 N2 O6; Mol wt: 500.4271

M.p. 181-3 °C.

ACTION – Antineoplastic agent, a purine derivative of L-ascorbic acid with cytostatic activity against a number of malignant cell lines such as pancreatic carcinoma MiaPaCa2 (IC_{50} = 30 μ M), breast carcinoma MCF-7 (IC_{50} = 40 μ M), cervical carcinoma HeLa (IC_{50} = 20 μ M), laryngeal carcinoma Hep2 (IC_{50} = 40 μ M), murine leukemia L1210/0 (IC_{50} = 2.0 μ M), murine mammary carcinoma FM3A/0 (IC_{50} = 3.6 μ M) and human lymphocyte Molt4/C8 and CEM/0 cells (IC_{50} = 0.9 and 1.6 μ M, respectively). Compound also showed antiviral activity against varicella-zoster virus (IC_{50} = 0.3-0.5 μ M) and cytomegalovirus (IC_{50} = 0.4-0.5 μ M), but at concentrations only slightly lower than those exerting cytotoxic effects (CC_{50} = 1 μ M).

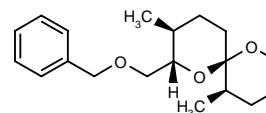
SOURCES – Rega Institute for Medical Research, Leuven (BE); Rudjer Boskovic Institute, Zagreb (HR); University of Zagreb, Zagreb (HR).

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1. Raic-Malic, S. et al. *Novel pyrimidine and purine derivatives of L-ascorbic acid: Synthesis and biological evaluation*. *J Med Chem* 1999, 42(14): 2673.

278864

(2*S*,3*S*,6*R*,11*R*)-2-(Benzyloxymethyl)-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane



C19 H28 O3; Mol wt: 304.4272

ACTION – Cytotoxic agent (LC_{50} = 14 μ M against human lymphoblastic leukemia Jurkat cells), a potent apoptosis inducer devoid of phosphatase-inhibitory activity.

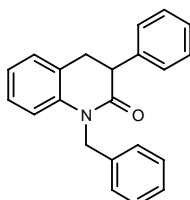
SOURCE – Hokkaido University, Sapporo (JP).

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2. Oikawa, H. et al. *Highly regio- and stereoselective reductions of spiroketals*. Tetrahedron Lett 1993, 34(33): 5303.

279181

1-Benzyl-3-phenyl-3,4-dihydroquinolin-2(1H)-one



C22 H19 N O; Mol wt: 313.3981

Yellow solid.

ACTION – Antineoplastic agent, an isoquinolone derivative with cytotoxic activity against a number of human cancer cell lines such as lung A-549, ovarian SK-OV-3, melanoma SK-MEL-2 and colon HCT-15 tumor cells (ED_{50} = 4.4, 4.5, 5.7 and 6.7 μ g/ml, respectively).

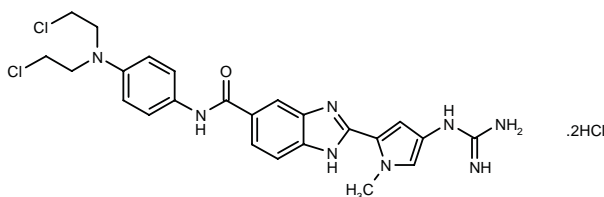
SOURCE – Chonnam National University, Kwangju (KR).

REFERENCES

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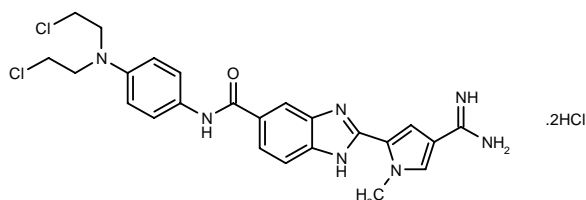
279221

N-[4-[Bis(2-chloroethyl)amino]phenyl]-2-(4-guanidino-1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamide dihydrochloride



C24 H26 Cl2 N8 O . 2HCl; Mol wt: 586.3522

ACTION – Antineoplastic agent that binds to DNA, proven active *in vitro* against murine B16 melanoma cells (IC_{50} = 3.5 μ g/ml). Another compound from this series of 2-pyrrolylbenzimidazole derivatives is:



279222: C24 H25 Cl2 N7 O . 2HCl

SOURCE – Mitsui Chemicals.

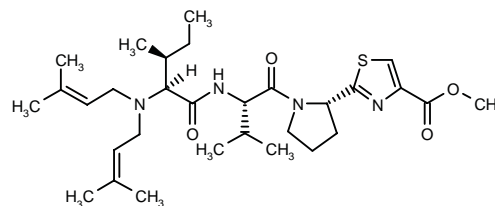
REFERENCES

1. Matsunaga, A. et al. (Mitsui Chemicals, Inc.) *Pyrrolylbenzimidazole derivs. having amidine or guanidine as side chain*. JP 99171886.

AERUGINOSAMIDE

278684

2-[1-[N,N-Bis(3-methyl-2-butenyl)-D-isoleucyl-L-valyl]-pyrrolidin-2(S)-yl]thiazole-4-carboxylic acid methyl ester



C30 H48 N4 O4 S; Mol wt: 560.7992

ACTION – Antineoplastic agent isolated from the cyanobacterium *Microcystis aeruginosa*, with cytotoxicity against human ovarian tumor A2780 cells and human leukemia K562 cells (ID_{50} = 2.9 and 5.2 μ M, respectively).

SOURCES – University of Aberdeen, Aberdeen (GB); Robert Gordon University, Aberdeen (GB).

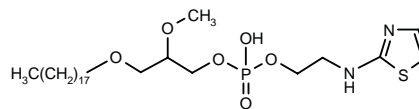
REFERENCES

1. Lawton, L.A. et al. *A bioactive modified peptide, aeruginosamide, isolated from the cyanobacterium Mycrocystis aeruginosa*. J Org Chem 1999, 64(14): 5329.

CPR-3005

278698

Phosphoric acid 2-methoxy-3-(octadecyloxy)propyl 2-(thiazol-2-ylamino)ethyl diester



C27 H53 N2 O6 P S; Mol wt: 564.7637

ACTION – A representative compound from a series of *N*-substituted glycerophosphoethanolamines with antineoplastic, antipsoriatic, antiinflammatory and PAF-antagonist activity. *In vitro*, compound inhibited the growth of human breast carcinoma MDA-MB-231 and human colon carcinoma HT-29 cell lines at concentrations above 3 μ M; in addition, it inhibited the proliferation of murine PAM-212 keratinocytes at concentrations above 10 μ M. Antiinflammatory activity was demonstrated by a marked inhibition of murine RAW 264.7 macrophage chemiluminescence at concentrations above 1 μ M. PAF antagonism was demonstrated by dose-dependent inhibition of PAF-induced bronchoconstriction in guinea pigs.

SOURCE – Clarion.

REFERENCES

1. Nair, H.K. (Clarion Pharmaceuticals Inc.) *N-het-substd. glycerophosphoethanolamines*. WO 9933851.

HSCS-1

278901

Human suppressor of cytokine signaling

ACTION – Novel human suppressor of cytokine signaling with potential in the diagnosis, prevention and treatment of cancer and immune disorders.

SOURCE – Incyte.

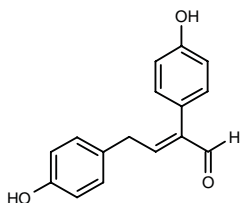
REFERENCES

1. Hillman, J.L. et al. (Incyte Pharmaceuticals, Inc.) *Suppressor of cytokine signaling*. WO 9923220.

S-1127

278540

2,4-Bis(4-hydroxyphenyl)-2-butenal



C16 H14 O3; Mol wt: 254.2836

ACTION – Antineoplastic and apoptosis-inducing agent shown to reduce the viability of human leukemia HL-60 cells in a concentration-dependent manner at 20-80 μ M.

SOURCE – Takara Shuzo.

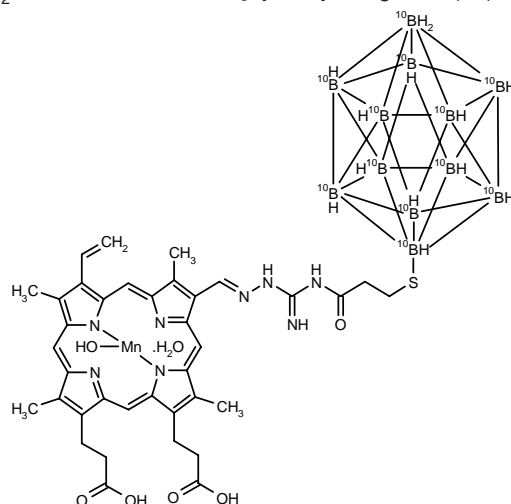
REFERENCES

1. Enoki, T. et al. (Takara Shuzo Co., Ltd.) *Apoptosis inducer*. WO 9929647.

STA-BX909

279196

Tetrahydrogen (OC-6-24)-aqua[1-[13-[[3-[3-(sulfanyl- κ S)propanoyl]guanidino]iminomethyl]-8-vinyl-3,7,12,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoato(4-)]-2,3,4,5,6,7,8,9,10,11,12-undecahydrododecaborato(7-)- $^{10}\text{B}_{12}$ - κ N 21 , κ N 22 , κ N 23 , κ N 24]hydroxymanganate(4-)



C37 H53 B12 Mn N8 O7 S; Mol wt: 928.8787

ACTION – Antineoplastic agent, a boronated porphyrin compound for boron neutron capture therapy; it exhibited active and selective uptake into rat glioma 9L cells both *in vitro* and *in vivo*, with increased boron concentrations with increasing exposure time *in vitro*. In a colony-forming assay with thermal neutron irradiation, compound was more cytotoxic than sodium borocaptate.

SOURCES – Nihon Schering; Toyo Hakka.

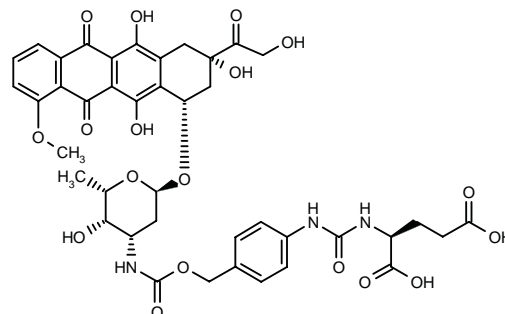
REFERENCES

1. Matsumura, A. et al. *A new boronated porphyrin (STA-BX909) for neutron capture therapy: An in vitro survival assay and in vivo tissue uptake study*. Cancer Lett 1999, 141(1-2): 203.

CANCER GENE THERAPY

277852

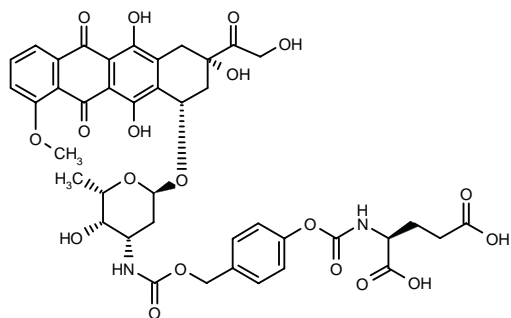
N-[4-[3-[1(*S*),3-Dicarboxypropyl]ureido]benzyloxycarbonyl]adriamycin



C41 H43 N3 O18; Mol wt: 865.7937

M.p. 182-4 °C.

ACTION – Antineoplastic agent, a self-immolative prodrug for suicide gene therapy that releases the cytotoxic anthracycline doxorubicin when cleaved by carboxypeptidase G2. Compound showed a 21-fold prodrug/drug cytotoxicity differential in control mammary carcinoma MDA-MB-361 cells, which was reduced to 5.4-fold in cells expressing carboxypeptidase G2 intracellularly and 10.7-fold in cells expressing the enzyme extracellularly. Another related compound is:



277854: C41 H42 N2 O19

SOURCE – Cancer Research Campaign.

REFERENCES

1. Niculescu-Duvaz, I. et al. *Self-immolative anthracycline prodrugs for suicide gene therapy*. J Med Chem 1999, 42(13): 2485.

HYB-102133

277117

20-Mer phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GGTTCCTACGGCCCCATACA-3'

ACTION – Antisense phosphorothioate oligodeoxynucleotide complementary to CDK4 mRNA, shown to concentration-dependently (0.1-1.0 μ M) reduce levels of CDK4 protein in human glioblastoma U-87 cells, with maximum inhibition of about 78%, whereas a control reverse-sequence oligonucleotide induced only non-specific inhibition reaching 27%. It is capable of regulating the growth of cells which have lost their G1-to-S-phase restriction point control and is thus useful for the treatment of tumors associated with aberrant expression of CDK4, cyclin D1 or p16. Another representative oligonucleotide is:

20-Mer phosphorothioate oligodeoxynucleotide whose sequence is: 5'-GAGCCGGTTCCTACGGCCCC-3'

HYB-102134 [277598]

SOURCE – Hybridon.

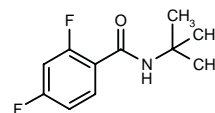
REFERENCES

1. Morrissey, D. and Von Hofe, E. (Hybridon, Inc.) *Antisense oligonucleotides specific for CDK4*. WO 9927087.

OCULAR MEDICATIONS

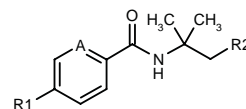
277506

N-(tert-Butyl)-2,4-difluorobenzamide



C11 H13 F2 N O; Mol wt: 213.2257

ACTION – Agent for the treatment of neuroretinal degeneration, proven active in a rat model of retinal damage induced by white light when given at 50 mg/kg i.p. Other compounds from this series of amide derivatives include the following:



Compound	R1	R2	A	Formula
277507	F	H	CH	C ₁₁ H ₁₄ FNO
277508	F	OH	CF	C ₁₁ H ₁₃ F ₂ NO ₂
277509	Cl	H	N	C ₁₀ H ₁₃ ClN ₂ O
277510	Cl	OH	N	C ₁₀ H ₁₃ ClN ₂ O ₂

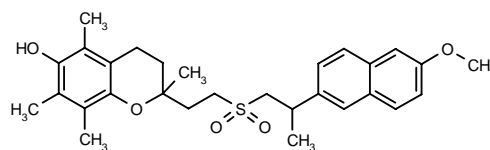
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Ikeda, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Amide derivs*. WO 9921543.

278576

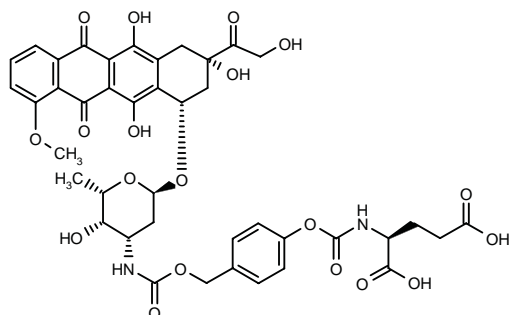
2-[2-[2-(6-Methoxynaphthalen-2-yl)propylsulfonyl]ethyl]-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-6-ol



C29 H36 O5 S; Mol wt: 496.6644

ACTION – Cytoprotective agent with potent anti-inflammatory, antiproliferative and antioxidant activity and various potential applications including the treatment of ocular inflammation associated with ophthalmic disease and ophthalmic surgery, the prevention of corneal haze following ocular surgery, for tissue preservation including cornea preservation during transplant procedures, and the adjunctive treatment of heart disease. Further potential uses for this compound include the prevention of secondary cataract formation, slowing the rate of neovascularization in conditions such as diabetic retinopathy and macular degeneration, and reducing the formation of atherosclerotic lesions. Other specifically claimed benzofurans and benzopyrans include the following:

ACTION – Antineoplastic agent, a self-immolative prodrug for suicide gene therapy that releases the cytotoxic anthracycline doxorubicin when cleaved by carboxypeptidase G2. Compound showed a 21-fold prodrug/drug cytotoxicity differential in control mammary carcinoma MDA-MB-361 cells, which was reduced to 5.4-fold in cells expressing carboxypeptidase G2 intracellularly and 10.7-fold in cells expressing the enzyme extracellularly. Another related compound is:



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SOURCE – Cancer Research Campaign.

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HYB-102133

277117

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HYB-102134 [277598]

SOURCE – HybriDon.

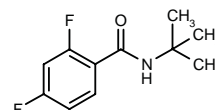
REFERENCES

1. Morrissey, D. and Von Hofe, E. (HybriDon, Inc.) *Antisense oligonucleotides specific for CDK4*. WO 9927087.

OCULAR MEDICATIONS

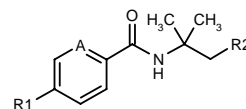
277506

N-(tert-Butyl)-2,4-difluorobenzamide



C11 H13 F2 N O; Mol wt: 213.2257

ACTION – Agent for the treatment of neuroretinal degeneration, proven active in a rat model of retinal damage induced by white light when given at 50 mg/kg i.p. Other compounds from this series of amide derivatives include the following:



Compound	R1	R2	A	Formula
277507	F	H	CH	C ₁₁ H ₁₄ FNO
277508	F	OH	CF	C ₁₁ H ₁₃ F ₂ NO ₂
277509	Cl	H	N	C ₁₀ H ₁₃ ClN ₂ O
277510	Cl	OH	N	C ₁₀ H ₁₃ ClN ₂ O ₂

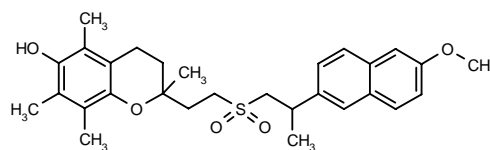
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Ikeda, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Amide derivs*. WO 9921543.

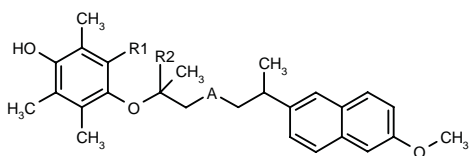
278576

2-[2-[2-(6-Methoxynaphthalen-2-yl)propylsulfonyl]ethyl]-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-6-ol



C29 H36 O5 S; Mol wt: 496.6644

ACTION – Cytoprotective agent with potent anti-inflammatory, antiproliferative and antioxidant activity and various potential applications including the treatment of ocular inflammation associated with ophthalmic disease and ophthalmic surgery, the prevention of corneal haze following ocular surgery, for tissue preservation including cornea preservation during transplant procedures, and the adjunctive treatment of heart disease. Further potential uses for this compound include the prevention of secondary cataract formation, slowing the rate of neovascularization in conditions such as diabetic retinopathy and macular degeneration, and reducing the formation of atherosclerotic lesions. Other specifically claimed benzofurans and benzopyrans include the following:



Compound	R1,R2	A	Formula
278577	-CH2-	-S-	C ₂₇ H ₃₂ O ₃ S
278578	-(CH2)2-	-S-	C ₂₈ H ₃₄ O ₃ S
278579	-(CH2)2-	-CH2S-	C ₂₉ H ₃₆ O ₃ S
278580	-(CH2)2-	-CH2SO-	C ₂₉ H ₃₆ O ₄ S

SOURCE – Alcon.

REFERENCES

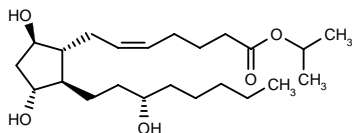
1. Hellberg, M.R. et al. (Alcon Laboratories, Inc.) *Benzofurans and benzopyrans as cytoprotective agents*. WO 9932474.

OSA-8302*

218529

13,14-Dihydroprostaglandin F_{2β} isopropyl ester

(5Z,9β,11α,15S)-9,11,15-Trihydroxyprost-5-en-1-oic acid isopropyl ester



C₂₃ H₄₂ O₅; Mol wt: 398.5880

ACTION – Prostaglandin F_{2β} derivative proven to dose-dependently reduce intraocular pressure in rabbits (0.006-0.1%), as well as in cynomolgus monkeys (0.02%) and cats (0.02%), with an effect comparable to that of the reference PhXA4 and more potent than UF-021 and timolol. Compound was devoid of a general hypotensive effect and did not reduce pupil diameter. Potentially useful for the treatment of glaucoma.

SOURCES – Ono; Santen.

REFERENCES

1. Miyazaki, T. et al. (Ono Pharmaceutical Co., Ltd.) *13,14-Dihydro-PGF_{2β} and its isopropyl ester*. CA 2125804, EP 628545, JP 95061965.
2. Nakata, K. et al. (Santen Pharmaceutical Co., Ltd.) *Therapeutic agents for retinal disease*. JP 96310955.
3. Matsugi, T. et al. *Ocular hypotensive effects of OSA-8302, a novel prostaglandin F_{2β} derivative, in animals*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 3564.

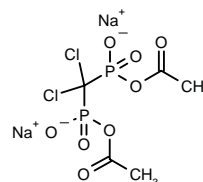
*Identified compound **218529** Drug Data Rep 1995, 017(05): 0486.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

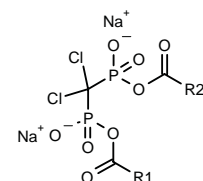
276091

Dicloromethylenebis(*O*-acetylphosphonic acid) disodium salt



C₅ H₆ Cl₂ Na₂ O₈ P₂; Mol wt: 372.9284

ACTION – Agent for the treatment of disorders of calcium metabolism such as bone disorders that acts as a prodrug of the known bisphosphonic acid clodronate⁺ and is reported to possess improved pharmacokinetic properties as compared to the parent drug due to an improved distribution coefficient, resulting in higher oral bioavailability. When tested *in vitro* in mouse calvaria, compound was even more effective than clodronate in inhibiting parathyroid hormone-induced bone resorption. Compound is also expected to be useful for the treatment of disorders related to pyrophosphate function in the organism such as bone cancer, ectopic calcifications, urolithiasis and rheumatoid arthritis. A representative compound from a series of methylenebisphosphonic acid derivatives, wherein the following are also included:



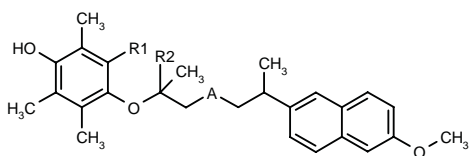
Compound	R1=R2	Formula
276092	Pr	C ₉ H ₁₄ Cl ₂ Na ₂ O ₈ P ₂
276093	Bu	C ₁₁ H ₁₈ Cl ₂ Na ₂ O ₈ P ₂
276094	t-Bu	C ₁₁ H ₁₈ Cl ₂ Na ₂ O ₈ P ₂
276095	Ph	C ₁₅ H ₁₀ Cl ₂ Na ₂ O ₈ P ₂
276096	i-Pr	C ₉ H ₁₄ Cl ₂ Na ₂ O ₈ P ₂
276097	C ₅ H ₁₁	C ₁₃ H ₂₂ Cl ₂ Na ₂ O ₈ P ₂

SOURCE – Leiras.

REFERENCES

1. Pohjala, E. et al. (Leiras Oy) *Novel methylenebisphosphonic acid derivs*. WO 9920634.

*Drug Data Rep 1986, 008(11): 1054.



Compound	R1,R2	A	Formula
278577	-CH2-	-S-	C ₂₇ H ₃₂ O ₃ S
278578	-(CH2)2-	-S-	C ₂₈ H ₃₄ O ₃ S
278579	-(CH2)2-	-CH2S-	C ₂₉ H ₃₆ O ₃ S
278580	-(CH2)2-	-CH2SO-	C ₂₉ H ₃₆ O ₄ S

SOURCE – Alcon.

REFERENCES

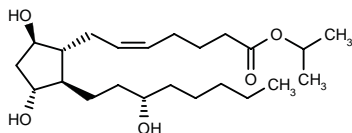
1. Hellberg, M.R. et al. (Alcon Laboratories, Inc.) *Benzofurans and benzopyrans as cytoprotective agents*. WO 9932474.

OSA-8302*

218529

13,14-Dihydroprostaglandin F_{2β} isopropyl ester

(5Z,9β,11α,15S)-9,11,15-Trihydroxyprost-5-en-1-oic acid isopropyl ester



C₂₃ H₄₂ O₅; Mol wt: 398.5880

ACTION – Prostaglandin F_{2β} derivative proven to dose-dependently reduce intraocular pressure in rabbits (0.006-0.1%), as well as in cynomolgus monkeys (0.02%) and cats (0.02%), with an effect comparable to that of the reference PhXA4 and more potent than UF-021 and timolol. Compound was devoid of a general hypotensive effect and did not reduce pupil diameter. Potentially useful for the treatment of glaucoma.

SOURCES – Ono; Santen.

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1. Miyazaki, T. et al. (Ono Pharmaceutical Co., Ltd.) *13,14-Dihydro-PGF_{2β} and its isopropyl ester*. CA 2125804, EP 628545, JP 95061965.
2. Nakata, K. et al. (Santen Pharmaceutical Co., Ltd.) *Therapeutic agents for retinal disease*. JP 96310955.
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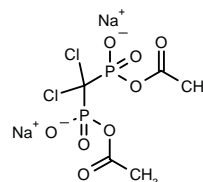
*Identified compound **218529** Drug Data Rep 1995, 017(05): 0486.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

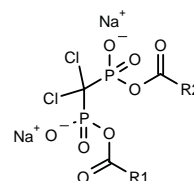
276091

Dicloromethylenebis(*O*-acetylphosphonic acid) disodium salt



C₅ H₆ Cl₂ Na₂ O₈ P₂; Mol wt: 372.9284

ACTION – Agent for the treatment of disorders of calcium metabolism such as bone disorders that acts as a prodrug of the known bisphosphonic acid clodronate⁺ and is reported to possess improved pharmacokinetic properties as compared to the parent drug due to an improved distribution coefficient, resulting in higher oral bioavailability. When tested *in vitro* in mouse calvaria, compound was even more effective than clodronate in inhibiting parathyroid hormone-induced bone resorption. Compound is also expected to be useful for the treatment of disorders related to pyrophosphate function in the organism such as bone cancer, ectopic calcifications, urolithiasis and rheumatoid arthritis. A representative compound from a series of methylenebisphosphonic acid derivatives, wherein the following are also included:



Compound	R1=R2	Formula
276092	Pr	C ₉ H ₁₄ Cl ₂ Na ₂ O ₈ P ₂
276093	Bu	C ₁₁ H ₁₈ Cl ₂ Na ₂ O ₈ P ₂
276094	t-Bu	C ₁₁ H ₁₈ Cl ₂ Na ₂ O ₈ P ₂
276095	Ph	C ₁₅ H ₁₀ Cl ₂ Na ₂ O ₈ P ₂
276096	i-Pr	C ₉ H ₁₄ Cl ₂ Na ₂ O ₈ P ₂
276097	C ₅ H ₁₁	C ₁₃ H ₂₂ Cl ₂ Na ₂ O ₈ P ₂

SOURCE – Leiras.

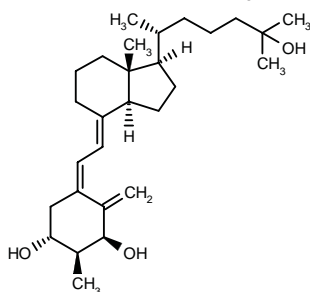
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*Drug Data Rep 1986, 008(11): 1054.

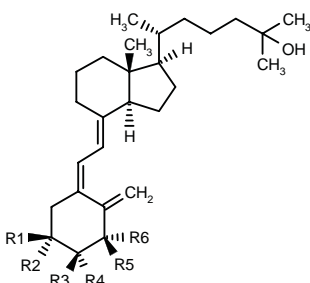
277237

1 α ,25-Dihydroxy-2 α -methylvitamin D₃



C28 H46 O3; Mol wt: 430.6684

ACTION – Vitamin D₃ derivative particularly useful for the treatment of osteoporosis. It was shown to induce the differentiation of HL-60 cells in the nitroblue tetrazolium reduction assay (about 90% at 1 μ M), demonstrating equivalent activity to 1 α ,25-dihydroxyvitamin D₃ (calcitriol). Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
277238	H	OH	H	Me	H	OH	C ₂₈ H ₄₆ O ₃
277239	OH	H	H	Me	OH	H	C ₂₈ H ₄₆ O ₃
277240	OH	H	H	Me	H	OH	C ₂₈ H ₄₆ O ₃
277241	H	OH	Me	H	H	OH	C ₂₈ H ₄₆ O ₃
277242	OH	H	Me	H	OH	H	C ₂₈ H ₄₆ O ₃
277243	OH	H	Me	H	H	OH	C ₂₈ H ₄₆ O ₃

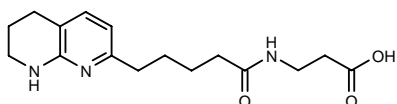
SOURCE – Teijin.

REFERENCES

1. Takayama, H. et al. (Teijin Ltd.) *Vitamin D3 derivs. and their preparation method*. JP 99116551.

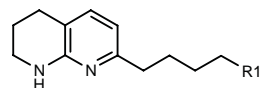
278022

3-[5-(5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl)pentan-amido]propionic acid

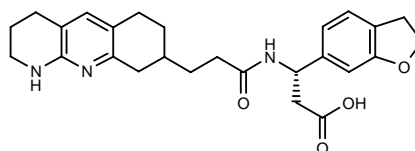


C16 H23 N3 O3; Mol wt: 305.3757

ACTION – Nonpeptide antagonist of integrin $\alpha_v\beta_3$, $\alpha_v\beta_5$ and/or $\alpha_v\beta_6$ receptors, potentially useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, wound healing, viral infections and tumor growth and metastasis. Other specifically claimed compounds include the following:



Compound	R1	Formula
278023	(S)-CONHCH(3-quinolyl)CH ₂ CO ₂ H	C ₂₅ H ₂₈ N ₄ O ₃
278027	(S)-(CH ₂) ₃ CH(NHCOPh)CO ₂ H	C ₂₄ H ₃₁ N ₃ O ₃
278028	(S)-2,3-dihydro-furo[3,2-b]pyridin-5-yl-CH(CH ₂ CO ₂ H)CH ₂ CH ₂	C ₂₄ H ₃₁ N ₃ O ₃



278024: C26 H31 N3 O4

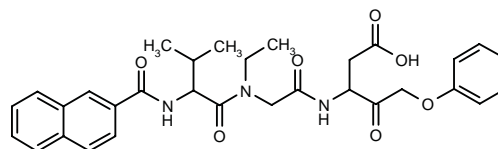
SOURCE – Merck & Co.

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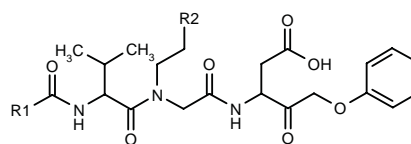
278536

3-[2-[N-Ethyl-3-methyl-2-(2-naphthylcarboxamido)-butyramido]acetamido]-4-oxo-5-phenoxy-pentanoic acid



C31 H35 N3 O7; Mol wt: 561.6315

ACTION – Agent for the treatment of osteoporosis, rheumatoid arthritis, septic shock, amyotrophic lateral sclerosis, stroke, inflammatory bowel disease and the like, an inhibitor of IL-1 β -converting enzyme (ICE, caspase-1). Other exemplified compounds from this series of alkyl-substituted glycine derivatives include the following:



Compound	R1	R2	Formula
278537	2-Naph	ethynyl	C ₃₃ H ₃₅ N ₃ O ₇
278538	2-Naph	2-oxazolyl-CH ₂	C ₃₅ H ₃₈ N ₄ O ₈
278539	CH ₂ CH ₂ Ph	1-imidazolyl-CH ₂	C ₃₃ H ₄₁ N ₅ O ₇

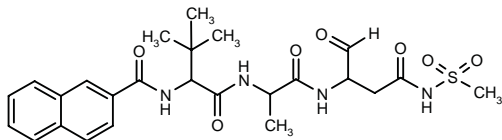
SOURCE – Yamanouchi.

REFERENCES

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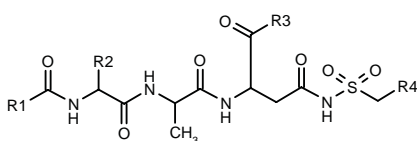
278550

*N*¹-[1-Formyl-3-(methylsulfonamido)-3-oxopropyl]-*N*²-[*N*-(2-naphthylcarbonyl)-DL-*tert*-leucyl]-DL-alaninamide

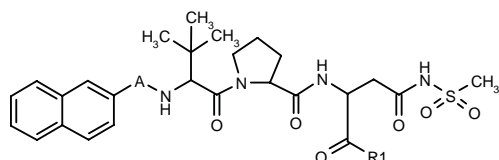


C25 H32 N4 O7 S; Mol wt: 532.6148

ACTION – Agent for the treatment of osteoporosis, rheumatoid arthritis, septic shock, amyotrophic lateral sclerosis, stroke, inflammatory bowel disease and the like, an inhibitor of IL-1 β -converting enzyme (ICE, caspase-1). Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
278551	2-Naph	t-Bu	2-thiazolyl	H	C ₂₈ H ₃₃ N ₅ O ₇ S ₂
278552	OCH ₂ Ph	i-Pr	CH ₂ OPh	H	C ₂₈ H ₃₆ N ₄ O ₉ S
278553	2-Pyr	i-Pr	2-thiazolyl	H	C ₂₂ H ₂₈ N ₆ O ₇ S ₂
278554	CH ₂ CH ₂ Ph	i-Pr	CH ₂ OPh	Me	C ₃₀ H ₄₀ N ₄ O ₈ S



Compound	R1	A	Formula
278555	H	CO	C ₂₇ H ₃₄ N ₄ O ₇ S
278556	2-benzoxazolyl	CO	C ₃₄ H ₃₇ N ₅ O ₈ S
278557	CH ₂ OPh	SO ₂	C ₃₃ H ₄₀ N ₄ O ₉ S ₂

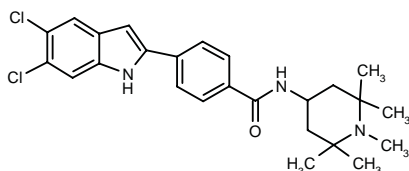
SOURCE – Yamanouchi.

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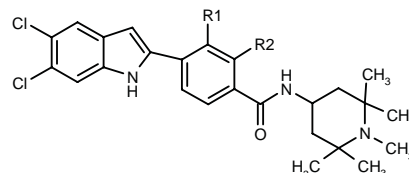
278659

4-(5,6-Dichloro-1*H*-indol-2-yl)-*N*-(1,2,2,6,6-pentamethylpiperidin-4-yl)benzamide



C25 H29 Cl₂ N₃ O; Mol wt: 458.4301

ACTION – Agent for the treatment of osteoporosis, Paget's disease, hyperparathyroidism and related diseases that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Compound was found to inhibit bafilomycin-sensitive ATPase in chicken osteoclasts with an IC₅₀ value of 0.096 μ M. In addition, compound was shown to exhibit selectivity for bafilomycin-sensitive ATPase in human osteoclasts relative to that in human kidney membranes, with IC₅₀ values of 0.25 and 1.25 μ M, respectively. Also reported to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity. Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	Formula
278660	OMe	H	C ₂₆ H ₃₁ Cl ₂ N ₃ O ₂
278661	H	OMe	C ₂₆ H ₃₁ Cl ₂ N ₃ O ₂

SOURCE – SmithKline Beecham.

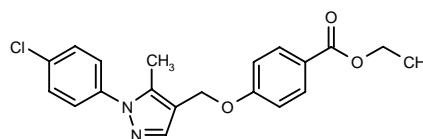
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TREATMENT OF LIPOPROTEIN DISORDERS

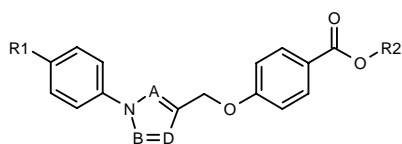
277623

4-[1-(4-Chlorophenyl)-5-methyl-1*H*-pyrazol-4-ylmethoxy]-benzoic acid ethyl ester



C20 H19 Cl N₂ O₃; Mol wt: 370.8341

ACTION – Dual fatty acid and cholesterol biosynthesis inhibitor (IC₅₀ = 6.36 and 7.49 μ M, respectively, in rat hepatic slices). In rats, the compound significantly reduced serum LDL cholesterol, triglycerides and phospholipids (22.3, 49.3 and 15.9%, respectively) at a dose of 30 mg/kg/day p.o. for 7 days. Other exemplified phenylcarboxylate derivatives are:



Compound	R1	R2	A	B	D	Formula
277624	H	Me	C(Me)	N	CH	C ₁₉ H ₁₈ N ₂ O ₃
277626	Cl	H	C(Me)	N	CH	C ₁₈ H ₁₅ ClN ₂ O ₃
277627	Cl	Me	N	C(Me)	N	C ₁₈ H ₁₆ ClN ₃ O ₃

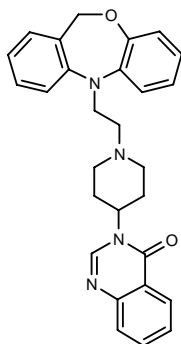
SOURCE – Taiho.

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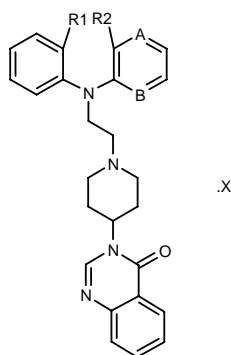
278542

3-[1-[2-(5,11-Dihydrodibenzo[*b,e*][1,4]oxazepin-5-yl)-ethyl]piperidin-4-yl]quinazolin-4(3*H*)-one



C₂₈H₂₈N₄O₂; Mol wt: 452.5552

ACTION – Agent for the treatment of atherosclerosis, pancreatitis, obesity, hypercholesterolemia, hypertriglyceridemia and hyperlipidemia, an inhibitor of microsomal triglyceride transfer protein (MTP; IC₅₀ = 0.07 μM) and apolipoprotein B (ApoB) secretion (IC₅₀ = 0.02 μM). *In vivo*, compound was shown to decrease triglyceride levels in rats with Triton WR-1339- and olive oil-induced hyperlipidemia at doses of 3 and 30 mg/kg p.o., respectively. Other compounds from this series of 3-piperidyl-4-oxoquinazoline derivatives include the following:



Compound	R1	R2	A	B	X	Formula
278543	Me	H	CH	CH	HCl	C ₂₈ H ₃₀ N ₄ O.HCl
278544	H	H	N	CH	HCl	C ₂₆ H ₂₄ N ₅ O.HCl

Compound	R1	R2	A	B	X	Formula
278545	Pr	H	CH	CH		C ₃₀ H ₃₄ N ₄ O
278546	i-Pr	H	CH	CH		C ₃₀ H ₃₄ N ₄ O
278547	-(CH ₂) ₂ -		CH	CH		C ₂₈ H ₃₀ N ₄ O
278548	Et	H	CH	N	2HCl	C ₂₈ H ₃₁ N ₅ O.2HCl
278549	Pr	H	CH	N		C ₂₉ H ₃₃ N ₅ O

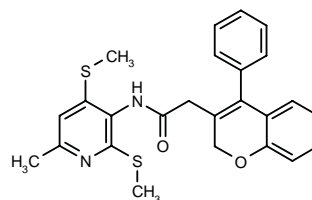
SOURCE – Japan Tobacco.

REFERENCES

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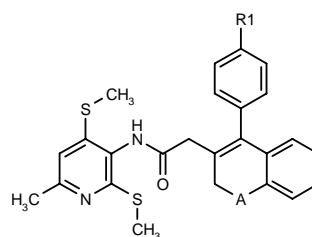
278691

N-[2,4-Bis(methylsulfanyl)-6-methylpyridin-3-yl]-2-(4-phenyl-2*H*-1-benzopyran-3-yl)acetamide



C₂₅H₂₄N₂O₂S₂; Mol wt: 448.6086

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of ACAT (IC₅₀ = 94 nM using enzyme from rat hepatic microsomes) shown to inhibit the intestinal absorption of cholesterol in rats with an ED₅₀ value of 0.005 mg/kg p.o. Cholesterol-lowering activity was demonstrated in cholesterol-fed rats (50% decrease at 0.78 mg/kg/day p.o. x 2 days) and rabbits (70% decrease at 0.1 mg/kg/day p.o. x 15 days). Other compounds from this series of *N*-phenylamide and *N*-pyridylamide derivatives include the following:



Compound	R1	A	Formula
278692	H	CH ₂	C ₂₆ H ₂₆ N ₂ O ₂ S ₂
278693	F	O	C ₂₆ H ₂₃ FN ₂ O ₂ S ₂

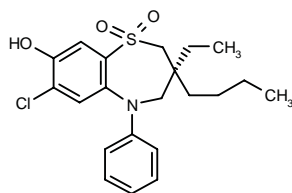
SOURCE – Merck KGaA.

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278874

3(S)-Butyl-7-chloro-3-ethyl-8-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine 1,1-dioxide



C21 H26 Cl N O3 S; Mol wt: 407.9594

ACTION – Agent for the treatment of hyperlipidemia and atherosclerosis, an inhibitor of ileal bile acid transport. *In vivo*, compound was found to inhibit intestinal bile acid reuptake in rats with an ED₃₀ of 0.048 mg/kg p.o., as measured by inhibition of ⁷⁵SeHCAAT fecal excretion. In addition, it was shown to lower cholesterol levels by 81, 56 and 48% at 0.3, 0.1 and 0.03 mg/kg p.o., respectively, in cholesterol- and cholic acid-fed rats. A specifically claimed compound from a series of benzothiazepine derivatives.

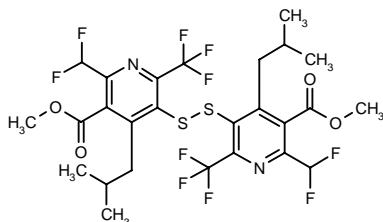
SOURCE – Glaxo Wellcome.

REFERENCES

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280002

5,5'-Dithiobis[2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)pyridine-3-carboxylic acid] dimethyl ester



C26 H26 F10 N2 O4 S2; Mol wt: 684.6134

ACTION – Hypolipidemic and antiatherosclerotic agent that acts by inhibiting cholesteryl ester transfer protein (CETP), as demonstrated *in vitro* (IC₅₀ = 1.5 μM) and *ex vivo* in hamsters. When tested in a chronic assay in cholesterol-fed hamsters at 38.5 mg/kg i.v. followed by an infusion of 1.3 mg/day using an Alzet pump, it produced a 30% reduction and a 26% increase in LDL and HDL cholesterol levels, respectively, on day 5, which persisted until emptying of the Alzet pump on day 8.

SOURCE – Searle.

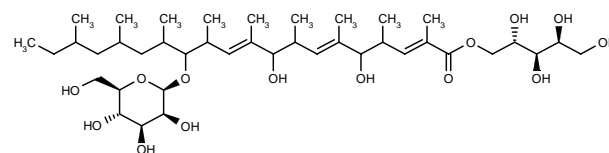
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ROSELIPIN 1A

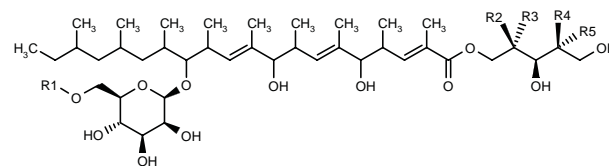
277759

5,9-Dihydroxy-13-(β-D-mannopyranosyloxy)-2,4,6,8,10,12,14,16,18-nonamethylcosa-2(E),6(E),10(E)-trienoic acid (2S,3R,4S)-2,3,4,5-tetrahydroxypentyl ester



C40 H72 O14; Mol wt: 776.9948

ACTION – Fungal metabolite for the treatment of hypertriglyceridemia, obesity and atherosclerosis, a diacylglycerol acyltransferase (DGAT) inhibitor isolated from the culture broth of the marine fungus *Gliocladium roseum* KF-1040; it inhibited DGAT in rat liver microsomes with an IC₅₀ value of 17 μM. Also reported to exert antimicrobial activity against *Saccharomyces cerevisiae* and *Aspergillus niger*. Other compounds isolated from this source are:



Compound	R1	R2	R3	R4	R5	Formula
Roselipin 1B [277760]	H	OH	H	H	OH	C ₄₀ H ₇₂ O ₁₄
Roselipin 2A [277761]	Ac	H	OH	OH	H	C ₄₂ H ₇₄ O ₁₅
Roselipin 2B [277762]	Ac	OH	H	H	OH	C ₄₂ H ₇₄ O ₁₅

SOURCE – Kitasato Institute, Tokyo (JP).

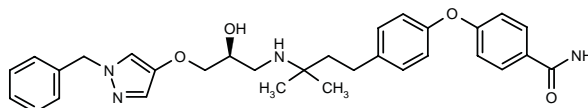
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

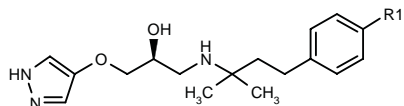
277422

4-[4-[3-[3-(1-Benzyl-1H-pyrazol-4-yloxy)-2(S)-hydroxy-propylamino]-3-methylbutyl]phenoxy]benzamide



C31 H36 N4 O4; Mol wt: 528.6494

ACTION – Selective β_3 -adrenoceptor agonist with potential in the treatment of type II diabetes and obesity. It was shown to be more active than isoproterenol in the cAMP assay in cells expressing the human β_3 -adrenoceptor, whereas it showed greatly reduced or no stimulation of β_1 - and β_2 -adrenoceptors. Other exemplified compounds are:



Compound	R1	Formula
277423	4-CONH2-PhO	C ₂₄ H ₃₀ N ₄ O ₄
277424	CONH2	C ₁₈ H ₂₆ N ₄ O ₃

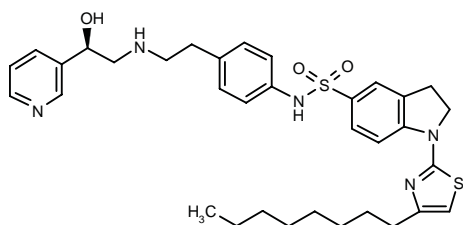
SOURCE – Lilly.

REFERENCES

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278085

N-[4-[2-[2(*R*)-Hydroxy-2-(pyridin-3-yl)ethylamino]ethyl]phenyl]-1-(4-octyl-2-thiazolyl)-2,3-dihydro-1*H*-indole-5-sulfonamide



C34 H43 N5 O3 S2; Mol wt: 633.8777

ACTION – Potent human β_3 -adrenoceptor agonist (EC_{50} = 0.93 nM for adenylyl cyclase activation; 86% of the maximal effect of isoproterenol) with 2800- and 1400-fold selectivity over β_1 - and β_2 -adrenoceptors (IC_{50} = 2600 and 1300 nM, respectively, in binding assays using membranes from CHO cells expressing cloned human receptors). Potentially useful for the treatment of obesity.

SOURCE – Merck & Co.

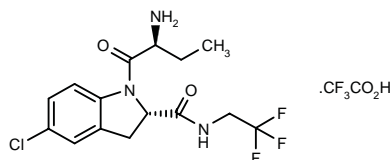
REFERENCES

1. Fisher, M.H. et al. (Merck & Co., Inc.) *Subst. sulfonamides as selective β_3 agonists for the treatment of diabetes and obesity*. EP 757674, JP 97512275, US 5541197, US 5561142, WO 9529159.

2. Mathvink, R.J. et al. *Potent, selective human beta3 adrenergic receptor agonists containing a substituted indoline-5-sulfonamide pharmacophore*. Bioorg Med Chem Lett 1999, 9(13): 1869.

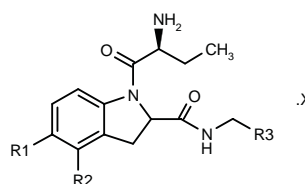
278638

1-[2(*S*)-Aminobutyryl]-5-chloro-*N*-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-indole-2(*S*)-carboxamide trifluoroacetate



C15 H17 Cl F3 N3 O2 . C2 H F3 O2; Mol wt: 477.7872

ACTION – Agent for the treatment of eating disorders, obesity and psychotic disorders that acts by inhibiting the cholecystokinin-inactivating peptidase tripeptidyl peptidase (TPP II; K_i = 0.40 nM). Other exemplified compounds from this series of 2,3-dihydro-1*H*-indole-2-carboxamide derivatives include the following:



Compound	R1	R2	R3	X	Isomer	Formula
278639	Cl	H	CH2Cl	CF3CO2H	S	C ₁₅ H ₁₅ Cl ₂ N ₃ O ₂ .C ₂ HF ₃ O ₂
278640	H	H	CH2SMe	CF3CO2H	S	C ₁₆ H ₂₃ N ₃ O ₂ S .C ₂ HF ₃ O ₂
278643	H	H	cyclopropyl	CF3CO2H	S	C ₁₇ H ₂₃ N ₃ O ₂ .C ₂ HF ₃ O ₂
278645	H	H	CF3	oxalate	S	C ₁₅ H ₁₈ F ₃ N ₃ O ₂ .C ₂ H ₂ O ₄
278646	OH	H	CF3	CF3CO2H		C ₁₅ H ₁₈ F ₃ N ₃ O ₃ .C ₂ HF ₃ O ₂
278647	H	Cl	CF3	CF3CO2H		C ₁₅ H ₁₇ ClF ₃ N ₃ O ₂ .C ₂ HF ₃ O ₂
278648	H	F	CF3	CF3CO2H		C ₁₅ H ₁₇ F ₄ N ₃ O ₂ .C ₂ HF ₃ O ₂
278649	OMe	H	CF3	CF3CO2H		C ₁₆ H ₂₀ F ₃ N ₃ O ₃ .C ₂ HF ₃ O ₂
278650	OCF3	H	CF3	CF3CO2H		C ₁₆ H ₁₇ F ₆ N ₃ O ₃ .C ₂ HF ₃ O ₂

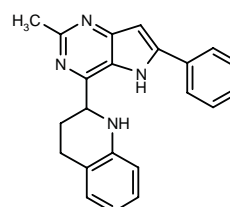
SOURCE – INSERM.

REFERENCES

1. Schwartz, J.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Tripeptidyl peptidase inhibitors*. WO 9933801.

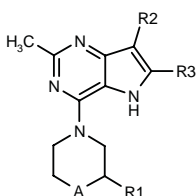
279989

2-(2-Methyl-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)-1,2,3,4-tetrahydroquinoline



C22 H20 N4; Mol wt: 340.4280

ACTION – Neuropeptide Y (NPY) receptor antagonist with potential in the treatment of eating disorders, obesity, diabetes, cancer, inflammatory disorders, depression, stress-related disorders and Alzheimer's disease. Compound was found to reduce NPY-induced food intake in satiated rats following intracerebroventricular injection. Other specifically claimed compounds from this series of bicyclic pyridine and pyrimidine derivatives include the following:



Compound	R1	R2	R3	A	Formula
279990	CH ₂ OH	H	Ph	CH ₂	C ₁₉ H ₂₂ N ₄ O
279991	H	H	2-thienyl	CH ₂	C ₁₆ H ₁₈ N ₄ S
279993	H	H	2,3,4-(Cl)3-Ph	CH ₂	C ₁₈ H ₁₇ Cl ₃ N ₄
279995	H	Me	4-MeO-Ph	CH ₂	C ₂₀ H ₂₄ N ₄ O
279996	H	H	7-MeO-2-benzofuryl	CH ₂	C ₂₁ H ₂₂ N ₄ O ₂
279998	H	H	4-(CF ₃ O)-Ph	CH ₂	C ₁₉ H ₁₉ F ₃ N ₄ O
280000	H	H	Ph	-N(2-furyl-CO)-	C ₂₂ H ₂₁ N ₅ O ₂

SOURCE – Amgen.

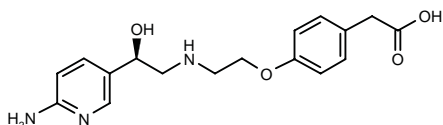
REFERENCES

1. Norman, M.H. et al. (Amgen Inc.) *Bicyclic pyridine and pyrimidine derivs. as neuropeptide Y receptor antagonists*. WO 9940091.

CP-331684*

245353

2-[4-[2-[2-(R)-(6-Amino-3-pyridinyl)-2-hydroxyethylamino]-ethoxy]phenyl]acetic acid



C17 H21 N3 O4; Mol wt: 331.3750

ACTION – Potent, selective and orally active β_3 -adrenoceptor agonist (EC_{50} = 0.4 and 0.07 μ M, respectively, for increase of intracellular cAMP in CHO cells transfected with human and rat β_3 -adrenoceptors) with high selectivity over human β_1 - and β_2 -adrenoceptors (EC_{50} = 18 and > 100 μ M, respectively); compound is more potent and more selective than both isoproterenol and BRL-37344. *In vivo*, orally administered compound was shown to increase oxygen consumption and plasma concentrations of both free fatty acids and glycerol (40-45% increase, at 10 mg/kg p.o.) in rats and to reduce glucose and insulin concentrations (25 and 60% reduction, respectively, at 10 mg/kg/day p.o. for 10 days) in *ob/ob* mice. Potentially useful for the treatment of type II diabetes and obesity, it has been selected for clinical trials.

SOURCE – Pfizer.

REFERENCES

1. Devries, K.M. et al. (Pfizer Inc.) *Process for subst. pyridines*. EP 938476, WO 9821184.
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3. Dow, R.L. (Pfizer Inc.) *β -Adrenergic agonists*. EP 824519, JP 99504649, WO 9635671.
4. Dow, R.L. et al. *Discovery of CP-331684 - an orally active, selective agonist of the human beta-3 adrenergic receptor*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-81.
5. Hargrove, D.M. et al. *Biological profile of CP-331,684 a novel orally active beta3-adrenergic agonist*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-82.

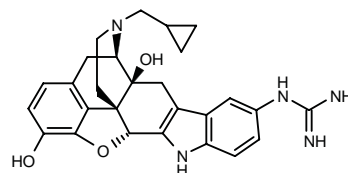
*Identified compound **245353** Drug Data Rep 1997, 019(03): 0247.

GNTI

279624

17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxy-5'-guanidino-6,7-didehydroindolo[2',3':6,7]morphinan

N-[(4b*S*,8*R*,8a*S*,14b*R*)-7-(Cyclopropylmethyl)-1,8a-dihydroxy-5,6,7,8,8a,9,14,14b-octahydro-4,8-methanobenzofuro[2,3-*a*]pyrido[4,3-*b*]carbazol-11-yl]guanidine



C27 H29 N5 O3; Mol wt: 471.5581

ACTION – A potent κ -opioid receptor antagonist (IC_{50} ratio [IC_{50} agonist in presence of 100 nM antagonist/ IC_{50} agonist alone] = 139.2 for ethylketazocine antagonism in guinea pig ileum) derived from naltrindole with high selectivity over μ - and δ -opioid receptors (IC_{50} ratio = 4.35 and 1.87, respectively, for morphine and DADLE antagonism in guinea pig ileum and mouse vas deferens). Potentially useful for the treatment of obesity, opioid dependence and psychosis.

SOURCE – University of Minnesota, Minneapolis, MN (US).

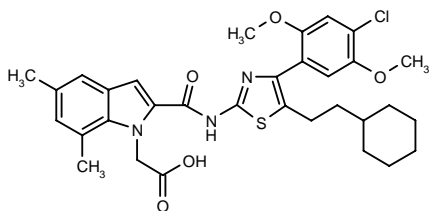
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1. Jones, R.M. et al. *Mutational evidence for a common kappa antagonist binding pocket in the wild-type kappa and mutant mu[K303E] opioid receptors*. J Med Chem 1998, 41(25): 4911.
2. Stevens, W.C. Jr. et al. *Naltrindole analogs as potent and selective kappa-opioid receptor antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 267.

SR-146131

259632

2-[2-[4-(4-Chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethyl-1*H*-indol-1-yl]acetic acid



C32 H36 Cl N3 O5 S; Mol wt: 610.1714

ACTION – Potent and selective cholecystokinin CCK₁ receptor agonist (IC₅₀ = 0.56 and 0.84 nM, respectively, for inhibition of [¹²⁵I]-BH-CCK-8S binding in membranes from 3T3 cells expressing human receptor membranes and rat pancreatic acini), showing 300-fold selectivity over CCK₂ receptors (IC₅₀ = 162 nM in CHO cells expressing human receptor). In a functional assay, compound showed full CCK₁ receptor-agonist activity and efficacy comparable to CCK-8S, as demonstrated by increase in intracellular Ca²⁺ levels in human CCK₁ receptor-expressing 3T3 cells (EC₅₀ = 1.38 and 0.75 nM, respectively, in cell culture and cell perfusion). Compound also fully stimulated inositol monophosphate formation (IC₅₀ = 18 nM), partially activated mitogen-activated protein kinase (MAPK; EC₅₀ = 290 nM) and enhanced the expression of the immediate early gene *krox 24*. In human IMR32 neuroblastoma cells, it bound to CCK₁ receptors with an IC₅₀ of 31 nM and exhibited partial agonist activity in increasing intracellular Ca²⁺ levels and inositol monophosphate formation. *In vivo*, compound inhibited gastric emptying and decreased gallbladder volume in mice (ED₅₀ = 66 and 2.7 µg/kg p.o.), dose-dependently reduced food intake in fasted rats (ED₅₀ = 0.43 g/kg p.o.), fasted gerbils (0.1-1 mg/kg p.o.) and marmosets maintained on a restricted diet (3-10 mg/kg p.o.), and antagonized neuropeptide Y (NPY)-induced stimulation of food intake in fasted rats (0.3-3 mg/kg p.o.). It was able to increase the number of Fos-positive cells in hypothalamic paraventricular nucleus of rats, indicating activation of the neurons implicated in the regulation of food intake by CCK via CCK₁ receptors. SR-146131 reduced locomotor activity in mice (ED₅₀ = 0.7 mg/kg p.o.), induced turning behaviour when applied into the striatum and antagonized fluphenazine-induced tardive dyskinesia in rats. Potentially useful for the treatment of obesity and motor disorders.

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Brodin, R. et al. (Sanofi SA) *Carboxamidothiazole derivs., preparation, pharmaceutical compsns. containing them*. FR 2768737, WO 9915525.
2. Bignon, E. et al. *SR146131: A new potent, orally active, and selective nonpeptide cholecystokinin subtype 1 receptor agonist. I: In vitro studies*. J Pharmacol Exp Ther 1999, 289(2): 742.
3. Bignon, E. et al. *SR146131: A new potent, orally active, and selective nonpeptide cholecystokinin subtype 1 receptor agonist. II: In vivo pharmacological characterization*. J Pharmacol Exp Ther 1999, 289(2): 752.

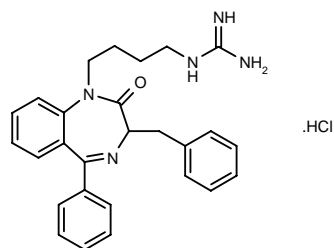
4. Bignon, E. et al. *SR146131: A new, potent, non-peptide orally active CCKA receptor agonist*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 872.

5. Schaeffer, P. et al. *Effects of SR146131, a novel CCKA receptor agonist, on IMR-32 human neuroblastoma cells*. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PT207.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

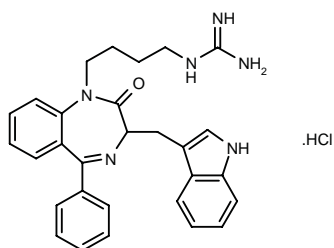
278588

(±)-*N*-[4-(3-Benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-1-yl)butyl]guanidine hydrochloride



C27 H29 N5 O . HCl; Mol wt: 476.0210

ACTION – Thrombopoietic agent that activates STAT5 (signal transducer and activator of transcription 5), thus exerting thrombopoietin (TPO) receptor-agonist activity. Potentially useful for regulating platelet production. Another compound from this series of benzodiazepine derivatives is:



278589: C29 H30 N6 O . HCl

SOURCE – Hokuriku.

REFERENCES

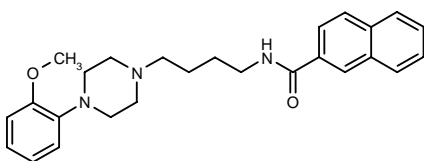
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TREATMENT OF POISONING AND DRUG DEPENDENCY

BP-897*

272697

N-[4-[4-(2-Methoxyphenyl)-1-piperazinyl]butyl]naphthalene-2-carboxamide



C26 H31 N3 O2; Mol wt: 417.5499

ACTION – Potent dopamine D₃ receptor partial agonist ($K_i = 0.92$ nM) with good to high selectivity over D₂, D₄ and D₁ receptors ($K_i = 61$, 300 and 3000 nM, respectively), α_1 - and α_2 -adrenoceptors ($K_i = 60$ and 83 nM, respectively), 5-HT_{1A} and 5-HT₇ receptors ($K_i = 84$ and 345 nM, respectively), and negligible affinity ($K_i > 1$ μ M) for muscarinic, histamine and opiate receptors. In a functional assay in NG 108-15 cells expressing the human D₃ receptor, compound exhibited partial agonist activity, as demonstrated by inhibition of forskolin-induced cAMP accumulation ($EC_{50} = 1.0$ nM, intrinsic activity about 60%); in CHO cells expressing D₂ receptors, compound exhibited relatively weak antagonist activity, as demonstrated by inhibition of quinpirole-induced mitogenesis ($K_i = 51$ nM). *In vivo*, compound inhibited cocaine-seeking behavior in rats, without any intrinsic, primary rewarding effects; its effects were suggested to involve potentiation of D₁ receptor-mediated effects in neurons in which D₁ and D₃ receptors are colocalized.

SOURCES – Bioprojet; INSERM.

REFERENCES

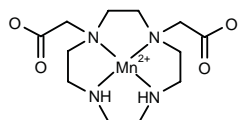
1. Wermuth, C.-G. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) 2-Naphthamide derivs. and their therapeutic applications. EP 779284, US 5872119.
2. Pilla, M. et al. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D₃ receptor agonist. Nature 1999, 400(6742): 371.

*Identified compound **272697** Drug Data Rep 1999, 021(03): 0209.

DIAGNOSTIC AGENTS

278878

[1,4,7,10-Tetraazacyclododecane-1,4-diacetato(2-)- $\kappa N^1, \kappa N^4, \kappa N^7, \kappa N^{10}, \kappa O^1, \kappa O^4$]manganese



C12 H22 Mn N4 O4; Mol wt: 341.2678

ACTION – Contrast agent with good tolerability and water solubility and low osmolality, suitable for the imaging of the gastrointestinal tract.

SOURCES – Bracco; Dibra.

REFERENCES

1. Geremia, R. et al. (Bracco SpA; Dibra SpA) 1,4,7,10-Tetraazacyclododecane-1,4-diacetic acid derivs. as chelating agents. WO 9935133.
2. Geremia, R. et al. (Bracco SpA; Dibra SpA) 1,4,7,10-Tetraazacyclododecane-1,4-diacetic acid. WO 9935134.

RB18A

278189

Cellular protein with an apparent molecular weight of 205 kDa, isolated after immunological screening of a cDNA expression library using the specific anti-p53 monoclonal antibody PAb1801

ACTION – A p53 regulatory polypeptide with potential in the diagnosis, prevention and treatment of p53-mediated disorders such as cancer, particularly colon, breast or ovarian cancer. In *in vitro* assays, it has been shown to share some functional properties with p53 protein such as DNA binding, homo-oligomerization, binding to p53 and inactivation of the sequence-specific DNA-binding function of p53.

SOURCE – INSERM.

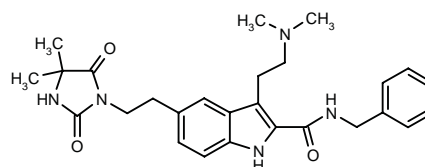
REFERENCES

1. Frade, R. (INSERM [Institut National de la Sante et de la Recherche Medicale]) p53 regulatory protein called RB18A and uses thereof. WO 9931231.

PHARMACOLOGICAL TOOLS

278352

N-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide



C27 H33 N5 O3; Mol wt: 475.5897

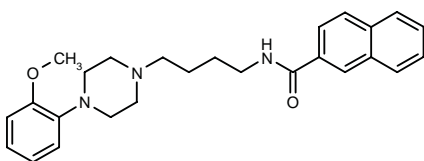
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TREATMENT OF POISONING AND DRUG DEPENDENCY

BP-897*

272697

N-[4-[4-(2-Methoxyphenyl)-1-piperazinyl]butyl]naphthalene-2-carboxamide



C26 H31 N3 O2; Mol wt: 417.5499

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SOURCES – Bioprojet; INSERM.

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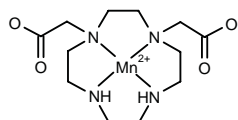
1. Wermuth, C.-G. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) 2-Naphthamide derivs. and their therapeutic applications. EP 779284, US 5872119.
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278189

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SOURCE – INSERM.

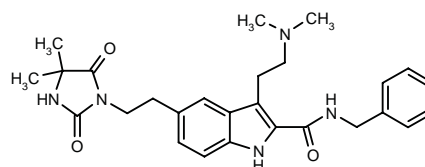
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PHARMACOLOGICAL TOOLS

278352

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C27 H33 N5 O3; Mol wt: 475.5897

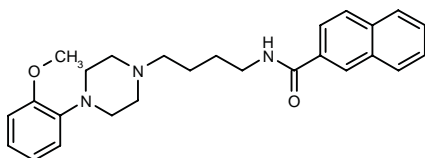
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TREATMENT OF POISONING AND DRUG DEPENDENCY

BP-897*

272697

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C26 H31 N3 O2; Mol wt: 417.5499

ACTION – Potent dopamine D₃ receptor partial agonist ($K_i = 0.92$ nM) with good to high selectivity over D₂, D₄ and D₁ receptors ($K_i = 61$, 300 and 3000 nM, respectively), α_1 - and α_2 -adrenoceptors ($K_i = 60$ and 83 nM, respectively), 5-HT_{1A} and 5-HT₇ receptors ($K_i = 84$ and 345 nM, respectively), and negligible affinity ($K_i > 1$ μ M) for muscarinic, histamine and opiate receptors. In a functional assay in NG 108-15 cells expressing the human D₃ receptor, compound exhibited partial agonist activity, as demonstrated by inhibition of forskolin-induced cAMP accumulation ($EC_{50} = 1.0$ nM, intrinsic activity about 60%); in CHO cells expressing D₂ receptors, compound exhibited relatively weak antagonist activity, as demonstrated by inhibition of quinpirole-induced mitogenesis ($K_i = 51$ nM). *In vivo*, compound inhibited cocaine-seeking behavior in rats, without any intrinsic, primary rewarding effects; its effects were suggested to involve potentiation of D₁ receptor-mediated effects in neurons in which D₁ and D₃ receptors are colocalized.

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1. Wermuth, C.-G. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]; Societe Civile Bioprojet) *2-Naphthamide derivs. and their therapeutic applications*. EP 779284, US 5872119.

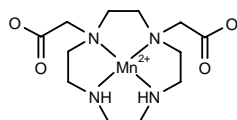
2. Pilla, M. et al. *Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist*. Nature 1999, 400(6742): 371.

*Identified compound **272697** Drug Data Rep 1999, 021(03): 0209.

DIAGNOSTIC AGENTS

278878

[1,4,7,10-Tetraazacyclododecane-1,4-diacetato(2-)- $\kappa N^1, \kappa N^4, \kappa N^7, \kappa N^{10}, \kappa O^1, \kappa O^4$]manganese



C12 H22 Mn N4 O4; Mol wt: 341.2678

ACTION – Contrast agent with good tolerability and water solubility and low osmolality, suitable for the imaging of the gastrointestinal tract.

SOURCES – Bracco; Dibra.

REFERENCES

1. Geremia, R. et al. (Bracco SpA; Dibra SpA) *1,4,7,10-Tetraazacyclododecane-1,4-diacetic acid derivs. as chelating agents*. WO 9935133.

2. Geremia, R. et al. (Bracco SpA; Dibra SpA) *1,4,7,10-Tetraazacyclododecane-1,4-diacetic acid*. WO 9935134.

RB18A

278189

Cellular protein with an apparent molecular weight of 205 kDa, isolated after immunological screening of a cDNA expression library using the specific anti-p53 monoclonal antibody PAb1801

ACTION – A p53 regulatory polypeptide with potential in the diagnosis, prevention and treatment of p53-mediated disorders such as cancer, particularly colon, breast or ovarian cancer. In *in vitro* assays, it has been shown to share some functional properties with p53 protein such as DNA binding, homo-oligomerization, binding to p53 and inactivation of the sequence-specific DNA-binding function of p53.

SOURCE – INSERM.

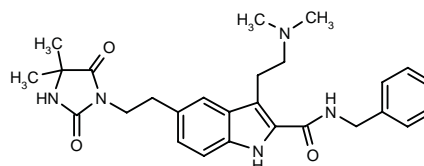
REFERENCES

1. Frade, R. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *p53 regulatory protein called RB18A and uses thereof*. WO 9931231.

PHARMACOLOGICAL TOOLS

278352

N-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide



C27 H33 N5 O3; Mol wt: 475.5897

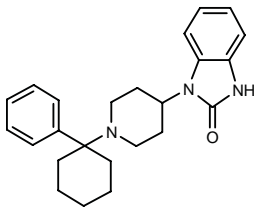
White powder, *m.p.* 182-3 °C.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

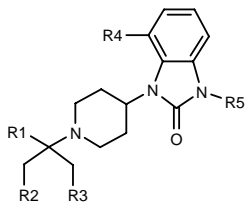
279207

1-[1-(1-Phenylcyclohexyl)piperidin-4-yl]-2,3-dihydro-1*H*-benzimidazol-2-one



C24 H29 N3 O; Mol wt: 375.5131

ACTION – Selective ORL1 receptor agonist potentially useful as an analgesic, antiinflammatory, diuretic, anesthetic, neuroprotective, antihypertensive and anxiolytic agent and as an agent for appetite control or hearing regulation. Other exemplified compounds from this series of 4-(2-keto-1-benzimidazoliny)piperidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
279208	Ph	H	H	H	H	C ₂₁ H ₂₅ N ₃ O
279209	2-thienyl	Me	Me	H	H	C ₂₁ H ₂₇ N ₃ OS
279210	Pr	-(CH ₂) ₆ -	H	H	H	C ₂₄ H ₃₇ N ₃ O
279211	3-MeO-Ph	-(CH ₂) ₄ -	H	H	H	C ₂₆ H ₃₃ N ₃ O ₂
279212	Ph	-(CH ₂) ₄ -	Cl	H	H	C ₂₅ H ₃₀ ClN ₃ O
279213	Ph	-CH ₂ CH=CHCH ₂ -	H	H	H	C ₂₅ H ₂₉ N ₃ O
279214	Ph	-(CH ₂) ₄ -	H	(CH ₂) ₃ NH ₂	H	C ₂₈ H ₃₈ N ₄ O
279215	Ph	-(CH ₂) ₄ -	H	4-[C(=NH)NH ₂]-1-Piz-CH ₂ CH ₂	H	C ₃₂ H ₄₅ N ₇ O

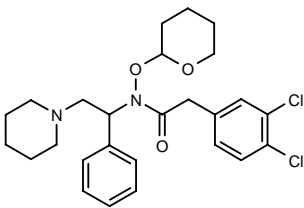
SOURCE – Pfizer.

REFERENCES

1. Ito, F. et al. (Pfizer Inc.) 4-(2-Keto-1-benzimidazoliny)piperidine cpds. as ORL1-receptor agonists. WO 9936421.

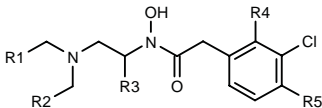
280400

2-(3,4-Dichlorophenyl)-*N*-[1-phenyl-2-(1-piperidiny)ethyl]-*N*-(tetrahydropyran-2-yloxy)acetamide



C26 H32 Cl2 N2 O3; Mol wt: 491.4558

ACTION – Selective κ -opioid receptor agonist reported to be useful as an analgesic, anesthetic, antiinflammatory, antitussive, diuretic and neuroprotective agent. Within this series of hydroxamic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
280401	-CH=CHCH ₂ -	Ph	Cl	H	H	C ₂₆ H ₃₀ Cl ₂ N ₂ O ₃
280402	vinyl	H	CH ₂ CH ₂ Ph	H	Cl	C ₂₂ H ₂₆ Cl ₂ N ₂ O ₂
280403	CH ₂ OH	H	CH ₂ CH ₂ Ph	H	Cl	C ₂₁ H ₂₆ Cl ₂ N ₂ O ₃

SOURCE – Pfizer.

REFERENCES

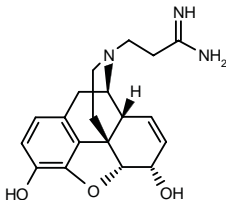
1. Ito, F. (Pfizer Inc.) Hydroxamic acid derivs. JP 99180950.

KRS-41

279574

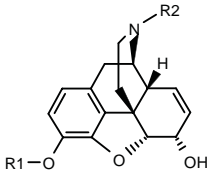
N-(2-Amidinoethyl)-7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol

3-(7,8-Didehydro-4,5α-epoxy-3,6α-dihoxymorphinan-*N*-yl)propionamidine

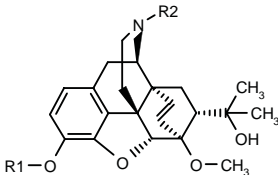


C19 H23 N3 O3; Mol wt: 341.4087

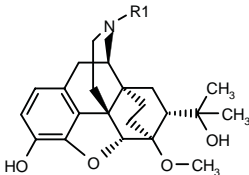
ACTION – A derivative of morphine with analgesic activity but free of the side effects associated with morphine by virtue of its selective affinity for peripheral opioid receptors; its selectivity is believed to be due to the presence of a highly polar group in its structure. Analgesic activity was demonstrated in the formalin and phenylbenzoquinone-induced writhing tests in mice, although at doses 3- and 5-fold higher, respectively, than morphine, and the absence of CNS effects was demonstrated in the Irwin test. Other compounds from this series of opioid derivatives include the following:



Compound	R1	R2	Formula
KRS-2-19 [279575]	H	C(=NH)NH2	C ₁₇ H ₁₉ N ₃ O ₃
KRS-2-63 [279580]	Me	CH2CH2C(=NH)NH2	C ₂₀ H ₂₅ N ₃ O ₃
KRS-2-47 [279581]	H	(CH2)3NHC(=NH)NH2	C ₂₀ H ₂₆ N ₄ O ₃



Compound	R1	R2	Formula
KRS-3-23-4 [279576]	H	C(=NH)NH2	C ₂₃ H ₂₉ N ₃ O ₄
KRS-3-28 [279577]	Me	CH2CH2C(=NH)NH2	C ₂₆ H ₃₅ N ₃ O ₄
KRS-3-56 [279579]	H	(CH2)3NHC(=NH)NH2	C ₂₆ H ₃₆ N ₄ O ₄
KRS-3-7 [279583]	Me	C(=NH)NH2	C ₂₆ H ₃₆ N ₄ O ₄



Compound	R1	Formula
KRS-3-30-2 [279578]	C(=NH)NH2	C ₂₃ H ₃₁ N ₃ O ₄
KRS-4-8 [281582]	(CH2)3NHC(=NH)NH2	C ₂₄ H ₃₁ N ₃ O ₄

SOURCES – Monash University, Clayton, Victoria (AU); Polychip.

REFERENCES

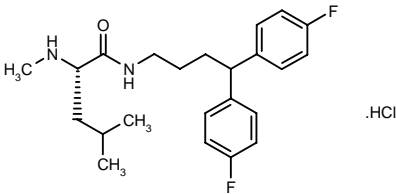
1. Jackson, R.W. et al. (Monash University;Polychip Pharmaceuticals Pty. Ltd.) *Therapeutic cpds.* WO 9938869.

PD-176078

279626

N-[4,4-Bis(4-fluorophenyl)butyl]-4-methyl-2(*S*)-(methylamino)pentanamide hydrochloride

*N*¹-[4,4-Bis(4-fluorophenyl)butyl]-*N*²-methyl-L-leucinamide hydrochloride



C23 H30 F2 N2 O . HCl; Mol wt: 424.9599

ACTION – Calcium channel blocker with good activity at both N- and L-type channels (IC₅₀ = 2.5 and 0.39 μM, respectively); electrophysiological studies demonstrated that compound also blocked Na⁺ and K⁺ channels with slightly lower or similar potency as for Ca²⁺ channels (IC₅₀ = 5.1, 9.9 and 1.3 μM, respectively). *In vivo*, compound showed anticonvulsant activity in the audiogenic seizure test in DBA/2 mice (ED₅₀ = 5.0 mg/kg i.v.) and analgesic properties, as demonstrated in the writhing test (ED₅₀ = 5.0 mg/kg i.v.), the formalin test (ED₅₀ = 15 mg/kg i.v.) and the Chung model (ED₅₀ = 70 mg/kg p.o.); at analgesic doses compound did not induce significant hypotension. Potentially useful as an analgesic and neuroprotective agent.

SOURCE – Warner-Lambert.

REFERENCES

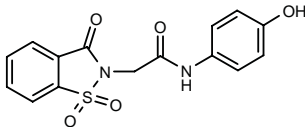
1. Connor, D.T. et al. (Warner-Lambert Co.) *Substd. diarylalkyl amides as calcium channel antagonists.* WO 9955688.

2. Song, Y. et al. *Novel N-type calcium channel antagonists: SAR studies on a series of benzhydrylalkyl amides and identification of PD 0176078 as a potent antagonist.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 265.

SCP-1

279596

N-(4-Hydroxyphenyl)-2-(1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl)acetamide



C15 H12 N2 O5 S; Mol wt: 332.3348

ACTION – Non-narcotic analgesic agent related to acetaminophen with comparable analgesic effect to the parent compound but without antipyretic activity, systemic or hepatic toxicity. Potentially useful particularly for the treatment of postoperative pain, pain in the elderly, chronic pain and pediatric pain where treatment with acetaminophen is contraindicated.

SOURCES – Universidad de Alcala, Alcala de Henares (ES); Louisiana State University, Baton Rouge, LA (US); St. Charles Pharmaceuticals.

REFERENCES

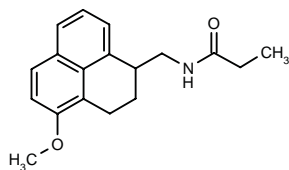
1. Bazan, N.G. and Alvarez-Builla Gomez, J. (LSU Medical Center Foundation) *New N-acylated 4-hydroxyphenylamine derivs. with analgesic properties and pharmaceutical compsns. containing them.* JP 99509520, US 5554636, WO 9632940.
2. Bazan, N.G. *Brain genes, drug discovery, and biotechnology.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst YCC-2.
3. Gonzalez-Martin, G. et al. *Hepatic kinetics of SCP-1 (N-[α -(1,2-benzisothiazol-3(2H)-ona-1,1-dioxide-2-yl)-acetyl]-p-aminophenol) compared with acetaminophen in isolated rat liver.* Eur J Pharm Biopharm 1998, 46(3): 293.
4. Minguez, J.M. et al. *Synthesis and design of potent analgesic compounds with low liver toxicity.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 183.
5. Paul, D. et al. *SCP-1: A novel acetaminophen-derived analgesic with no antipyretic or hepatotoxic activity.* Soc Neurosci Abst 1998, 24(Part 2): Abst 495.1.
6. Vaccarino, A.L. et al. *Analgesic and preemptive effects of SCP-1: A novel derivative of acetaminophen.* Soc Neurosci Abst 1999, 25(Part 2): Abst 771.12.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

278960

N-(4-Methoxy-2,3-dihydro-1*H*-phenalen-1-ylmethyl)-propionamide



C₁₈ H₂₁ N O₂; Mol wt: 283.3689

ACTION – Agent with strong affinity for melatonin receptors, particularly useful for the treatment of seasonal depression, sleep disorders, cardiovascular pathologies, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic and antiarrhythmic activity, and to have a powerful effect on circadian rhythms via the melatonergic system in animal models.

SOURCE – ADIR.

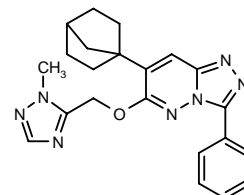
REFERENCES

1. Langlois, M. et al. (ADIR et Cie.) *Novel tricyclic cpds., preparation method and pharmaceutical compsns. containing same.* FR 2773798, WO 9936392.

ANXIOLYTICS

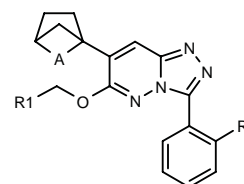
279100

7-(Bicyclo[2.2.1]hept-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine



C₂₂ H₂₃ N₇ O; Mol wt: 401.4717

ACTION – Agent for the treatment or prevention of CNS disorders, particularly anxiety and convulsions, with high affinity for the α_2 and/or α_3 subunit of the human GABA_A receptor (K_i = 100 nM or less for displacement of [³H]-flumazenil binding to human receptors). Other specifically claimed compounds within this series of triazolo-pyridazine derivatives include the following:



Compound	R1	R2	A	Formula
279101	1-Me-1,2,4-triazol-3-yl	H	-(CH ₂) ₂ -	C ₂₂ H ₂₃ N ₇ O
279102	2-Pyr	H	-(CH ₂) ₂ -	C ₂₄ H ₂₃ N ₅ O
279103	6-Me-2-Pyr	H	-(CH ₂) ₂ -	C ₂₅ H ₂₅ N ₅ O
279104	3-Me-2-Pyr	H	-(CH ₂) ₂ -	C ₂₅ H ₂₅ N ₅ O
279105	1-Me-1,2,4-triazol-5-yl	F	-CH ₂ -	C ₂₁ H ₂₀ FN ₇ O
279106	1-Me-1,2,4-triazol-3-yl	F	-CH ₂ -	C ₂₁ H ₂₀ FN ₇ O

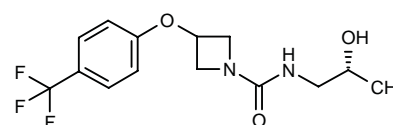
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors.* WO 9936423.

279532

N-[2(*R*)-Hydroxypropyl]-3-[4-(trifluoromethyl)phenoxy]-azetidine-1-carboxamide



C₁₄ H₁₇ F₃ N₂ O₃; Mol wt: 318.2933

ACTION – Non-narcotic analgesic agent related to acetaminophen with comparable analgesic effect to the parent compound but without antipyretic activity, systemic or hepatic toxicity. Potentially useful particularly for the treatment of postoperative pain, pain in the elderly, chronic pain and pediatric pain where treatment with acetaminophen is contraindicated.

SOURCES – Universidad de Alcala, Alcala de Henares (ES); Louisiana State University, Baton Rouge, LA (US); St. Charles Pharmaceuticals.

REFERENCES

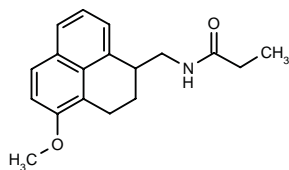
1. Bazan, N.G. and Alvarez-Builla Gomez, J. (LSU Medical Center Foundation) *New N-acylated 4-hydroxyphenylamine derivs. with analgesic properties and pharmaceutical compsns. containing them*. JP 99509520, US 5554636, WO 9632940.
2. Bazan, N.G. *Brain genes, drug discovery, and biotechnology*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst YCC-2.
3. Gonzalez-Martin, G. et al. *Hepatic kinetics of SCP-1 (N-[α -(1,2-benzisothiazol-3(2H)-ona-1,1-dioxide-2-yl)-acetyl]-p-aminophenol) compared with acetaminophen in isolated rat liver*. Eur J Pharm Biopharm 1998, 46(3): 293.
4. Minguez, J.M. et al. *Synthesis and design of potent analgesic compounds with low liver toxicity*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 183.
5. Paul, D. et al. *SCP-1: A novel acetaminophen-derived analgesic with no antipyretic or hepatotoxic activity*. Soc Neurosci Abst 1998, 24(Part 2): Abst 495.1.
6. Vaccarino, A.L. et al. *Analgesic and preemptive effects of SCP-1: A novel derivative of acetaminophen*. Soc Neurosci Abst 1999, 25(Part 2): Abst 771.12.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

278960

N-(4-Methoxy-2,3-dihydro-1*H*-phenalen-1-ylmethyl)-propionamide



C18 H21 N O2; Mol wt: 283.3689

ACTION – Agent with strong affinity for melatonin receptors, particularly useful for the treatment of seasonal depression, sleep disorders, cardiovascular pathologies, insomnia and fatigue due to time changes, appetite disorders and obesity. It is reported to exert anxiolytic and antiarrhythmic activity, and to have a powerful effect on circadian rhythms via the melatonergic system in animal models.

SOURCE – ADIR.

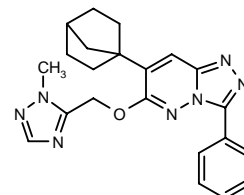
REFERENCES

1. Langlois, M. et al. (ADIR et Cie.) *Novel tricyclic cpds., preparation method and pharmaceutical compsns. containing same*. FR 2773798, WO 9936392.

ANXIOLYTICS

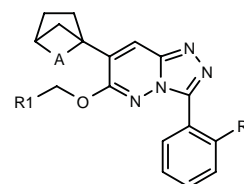
279100

7-(Bicyclo[2.2.1]hept-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine



C22 H23 N7 O; Mol wt: 401.4717

ACTION – Agent for the treatment or prevention of CNS disorders, particularly anxiety and convulsions, with high affinity for the α_2 and/or α_3 subunit of the human GABA_A receptor (K_i = 100 nM or less for displacement of [³H]-flumazenil binding to human receptors). Other specifically claimed compounds within this series of triazolo-pyridazine derivatives include the following:



Compound	R1	R2	A	Formula
279101	1-Me-1,2,4-triazol-3-yl	H	-(CH2)2-	C ₂₂ H ₂₃ N ₇ O
279102	2-Pyr	H	-(CH2)2-	C ₂₄ H ₂₃ N ₅ O
279103	6-Me-2-Pyr	H	-(CH2)2-	C ₂₅ H ₂₅ N ₅ O
279104	3-Me-2-Pyr	H	-(CH2)2-	C ₂₅ H ₂₅ N ₅ O
279105	1-Me-1,2,4-triazol-5-yl	F	-CH2-	C ₂₁ H ₂₀ FN ₇ O
279106	1-Me-1,2,4-triazol-3-yl	F	-CH2-	C ₂₁ H ₂₀ FN ₇ O

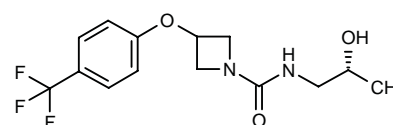
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9936423.

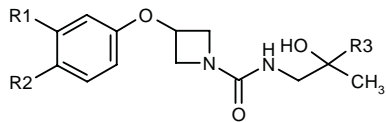
279532

N-[2(*R*)-Hydroxypropyl]-3-[4-(trifluoromethyl)phenoxy]-azetidine-1-carboxamide



C14 H17 F3 N2 O3; Mol wt: 318.2933

ACTION – Anxiolytic agent and anticonvulsant with good aqueous solubility, proven to protect against convulsions elicited by 3-mercaptopropionic acid (3-MPA) in mice at 30 mg/kg p.o. Other compounds from this series of azetidine-carboxamide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
279533	H	t-Bu	H	R	C ₁₇ H ₂₆ N ₂ O ₃
279534	H	Cl	H	R	C ₁₃ H ₁₇ ClN ₂ O ₃
279535	H	Cl	H	S	C ₁₃ H ₁₇ ClN ₂ O ₃
279536	H	Cl	Me		C ₁₄ H ₁₉ ClN ₂ O ₃
279537	H	F	H	R	C ₁₃ H ₁₇ FN ₂ O ₃
279538	Cl	Cl	H	R	C ₁₃ H ₁₆ Cl ₂ N ₂ O ₃

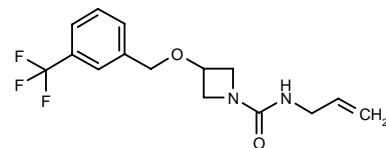
SOURCE – Cerebrus.

REFERENCES

1. Adams, D.R. et al. (Cerebrus Ltd.) *Azetidinecarboxamide derivs. for the treatment of CNS disorders*. WO 9937614.

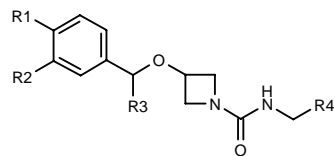
279539

N-Allyl-3-[3-(trifluoromethyl)benzyloxy]azetidine-1-carboxamide



C15 H17 F3 N2 O2; Mol wt: 314.3053

ACTION – Agent for the treatment of CNS disorders, particularly anxiety and epilepsy, shown to exhibit potent anticonvulsant activity against 3-mercaptopropionic acid (3-MPA)-induced seizures in mice, where it increased seizure threshold (measured in terms of mg/kg i.v. of 3-MPA required to evoke a seizure response) from 15.6 to 129.3 when given at 30 mg/kg p.o. Compound shows affinity for the GABA_A receptor (IC₅₀ = 87 μM against [³⁵S]-TBPS binding to rat forebrain membranes). Other compounds from this series of azetidinecarboxamide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279540	Cl	H	H	vinyl	C ₁₄ H ₁₇ ClN ₂ O ₂
279541	Cl	Cl	H	vinyl	C ₁₄ H ₁₆ Cl ₂ N ₂ O ₂
279542	CF3	H	H	vinyl	C ₁₆ H ₁₇ F ₃ N ₂ O ₂
279543	F	H	H	vinyl	C ₁₄ H ₁₇ FN ₂ O ₂
279544	Cl	H	4-Cl-Ph	vinyl	C ₂₀ H ₂₀ Cl ₂ N ₂ O ₂
279545	Cl	H	4-Cl-Ph	(R)-CH(OH)Me	C ₂₀ H ₂₂ Cl ₂ N ₂ O ₃

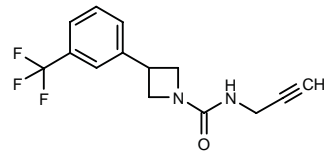
SOURCE – Cerebrus.

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1. Adams, D.R. et al. (Cerebrus Ltd.) *Azetidinecarboxamide derivs. for treating CNS disorders*. WO 9937612.

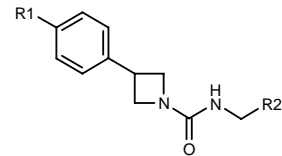
279546

N-(Prop-2-ynyl)-3-[3-(trifluoromethyl)phenyl]azetidine-1-carboxamide



C14 H13 F3 N2 O; Mol wt: 282.2637

ACTION – Agent for the treatment of CNS disorders, particularly anxiety and epilepsy, shown to exhibit potent anticonvulsant activity against 3-mercaptopropionic acid (3-MPA)-induced seizures in mice, where it increased seizure threshold (measured in terms of mg/kg i.v. of 3-MPA required to evoke a seizure response) from 17.2 to > 200.0 when given at 30 mg/kg p.o. Other compounds from this series of azetidinecarboxamide derivatives include the following:



Compound	R1	R2	Formula
279547	F	ethynyl	C ₁₃ H ₁₃ FN ₂ O
279548	F	(R)-CH(OH)Me	C ₁₃ H ₁₇ FN ₂ O ₂
279549	Cl	ethynyl	C ₁₃ H ₁₃ ClN ₂ O
279550	F	(S)-CH(OH)Me	C ₁₃ H ₁₇ FN ₂ O ₂
279551	CF3	(S)-CH(OH)Me	C ₁₄ H ₁₇ F ₃ N ₂ O ₂

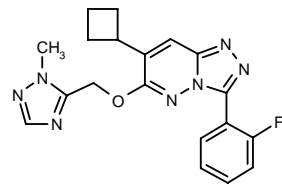
SOURCE – Cerebrus.

REFERENCES

1. Adams, D.R. et al. (Cerebrus Ltd.) *Azetidinecarboxamide derivs. for treating CNS disorders*. WO 9937613.

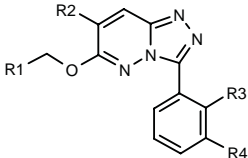
279558

7-Cyclobutyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine



C19 H18 F N7 O; Mol wt: 379.3972

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α 2 and/or α 3 subunits of the human GABA_A receptor relative to the α 1 subunit, and therefore expected to be associated with a reduced propensity to cause sedation, reported to possess good oral bioavailability. Compound is reported to have K_i values for displacement of [³H]-flumazenil from the α 2 and/or α 3 subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of triazolopyridazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279559	1-Me-1,2,4-triazol-3-yl	cyclobutyl	F	H	C ₁₉ H ₁₈ FN ₇ O
279560	1-Me-1,2,4-triazol-5-yl	cyclobutyl	H	F	C ₁₉ H ₁₈ FN ₇ O
279561	1-Me-1,2,4-triazol-5-yl	t-BuCH2	F	H	C ₂₀ H ₂₂ FN ₇ O
279562	1-Me-1,2,4-triazol-5-yl	i-Bu	F	H	C ₁₉ H ₂₀ FN ₇ O
279563	1-Me-1,2,4-triazol-5-yl	i-BuCH2	F	H	C ₂₀ H ₂₂ FN ₇ O
279564	1-Me-1,2,4-triazol-5-yl	4-Me-4-THP	F	H	C ₂₁ H ₂₂ FN ₇ O ₂
279565	1-Me-1,2,4-triazol-3-yl	4-Me-4-THP	F	H	C ₂₁ H ₂₂ FN ₇ O ₂
279566	1-Me-1,2,4-triazol-5-yl	1-Me-4,4-(F)2-cyclohexyl	F	H	C ₂₂ H ₂₂ F ₃ N ₇ O

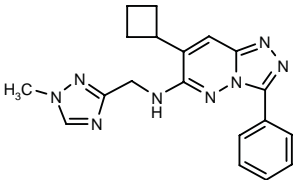
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937644.

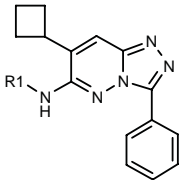
279567

N-(7-Cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-*N*-(1-methyl-1*H*-1,2,4-triazol-3-ylmethyl)amine



C19 H20 N8; Mol wt: 360.4230

ACTION – Anxiolytic agent and anticonvulsant with selective affinity for the α 2 and/or α 3 subunits of the human GABA_A receptor relative to the α 1 subunit, and therefore expected to be associated with a reduced propensity to cause sedation. Compound is reported to possess K_i values for displacement of [³H]-flumazenil binding from the α 2 and/or α 3 subunit of the human GABA_A receptor of 100 nM or less. Other specifically claimed compounds from this series of triazolopyridazine derivatives include the following:



Compound	R1	Formula
279568	Me	C ₁₆ H ₁₇ N ₅
279569	2-Pyr-CH2	C ₂₁ H ₂₀ N ₆
279570	(CH2)3N(Me)2	C ₂₀ H ₂₆ N ₆
279571	1-Piz-CH2CH2	C ₂₁ H ₂₇ N ₇

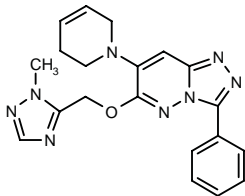
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Madin, A. and Owens, A.P. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937645.

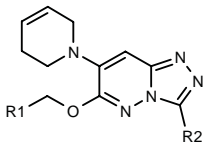
279639

6-(1-Methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-phenyl-7-(1,2,3,6-tetrahydropyridin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine



C20 H20 N8 O; Mol wt: 388.4330

ACTION – Selective GABA_A receptor ligand with particularly high affinity for α 2 and α 3 subunits, expected to be effective in the treatment of anxiety, convulsions and other CNS disorders with a reduced liability for sedation. Other specifically claimed substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives include the following:



Compound	R1	R2	Formula
279640	1-Me-1,2,4-triazol-3-yl	Ph	C ₂₀ H ₂₀ N ₈ O
279641	1-Me-1,2,4-triazol-5-yl	2,4-(F)2-Ph	C ₂₀ H ₁₈ F ₂ N ₈ O
279642	1-Me-1,2,4-triazol-5-yl	3-Pyr	C ₁₉ H ₁₉ N ₉ O
279643	3-Me-2-Pyr	3-Pyr	C ₂₂ H ₂₁ N ₇ O

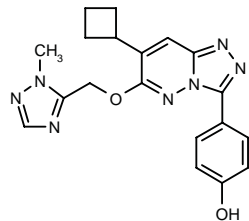
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Harrison, T. and Sparey, T.J. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937649.

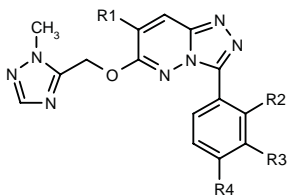
279644

4-[7-Cyclobutyl-6-(1-methyl-1*H*-1,2,4-triazol-5-yl)methoxy]-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol



C19 H19 N7 O2; Mol wt: 377.4061

ACTION – Selective GABA_A receptor ligand with particularly high affinity for α2 and α3 subunits, and therefore expected to be effective in the treatment of anxiety, convulsions and other CNS disorders, with a reduced liability for sedation. Other specifically claimed substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
279645	cyclobutyl	H	OH	H	C ₁₉ H ₁₉ N ₇ O ₂
279646	cyclobutyl	OH	H	H	C ₁₉ H ₁₉ N ₇ O ₂
279647	1-pyrrolidinyl	H	H	OH	C ₁₉ H ₂₀ N ₈ O ₂

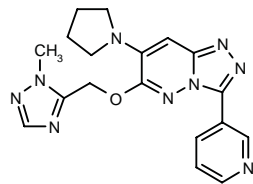
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Harrison, T. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937648.

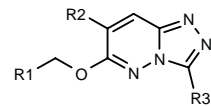
279648

6-(1-Methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-(3-pyridinyl)-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine



C18 H19 N9 O; Mol wt: 377.4101

ACTION – Selective GABA_A receptor ligand with particularly high affinity for α2 and α3 subunits, and therefore expected to be effective in the treatment of anxiety, convulsions and other CNS disorders, with a reduced liability for sedation. Other specifically claimed substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives include the following:



Compound	R1	R2	R3	Formula
279649	1-Me- -1,2,4-triazol-5-yl	cyclobutyl	3-Pyr	C ₁₈ H ₁₈ N ₈ O
279650	1-Me- -1,2,4-triazol-5-yl	1-Me- -cyclopentyl	3-Pyr	C ₂₀ H ₂₂ N ₈ O
279651	1-Me- -1,2,4-triazol-5-yl	cyclobutyl	3-(3-Pyr)-Ph	C ₂₄ H ₂₂ N ₈ O
279652	1-Me- -1,2,4-triazol-5-yl	1-pyrrolidinyl	3-(3-Pyr)-Ph	C ₂₄ H ₂₃ N ₉ O
279653	1-Me- -1,2,4-triazol-5-yl	1-Me- -cyclopentyl	3-(3-Pyr)-Ph	C ₂₆ H ₂₆ N ₈ O
279654	3-Me-2-Pyr	cyclobutyl	3-Pyr	C ₂₁ H ₂₀ N ₈ O

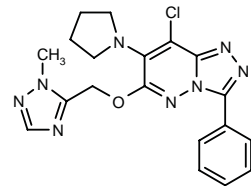
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Harrison, T. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937647.

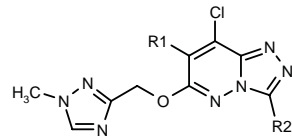
279655

8-Chloro-6-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy)-3-phenyl-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine



C19 H19 Cl N8 O; Mol wt: 410.8671

ACTION – Selective GABA_A receptor ligand with particularly high affinity for α2 and α3 subunits, expected to be effective in the treatment of anxiety, convulsions and other CNS disorders, with a reduced liability for sedation. Other specifically claimed substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives include the following:



Compound	R1	R2	Formula
279656	4-morpholinyl	2-thienyl	C ₁₇ H ₁₇ ClN ₈ O ₂ S
279657	1-pyrrolidinyl	Ph	C ₁₉ H ₁₉ ClN ₈ O

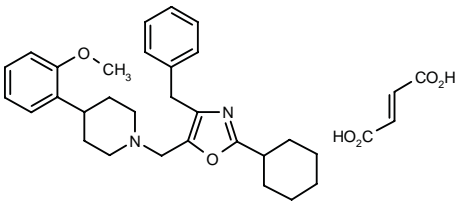
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Triazolo-pyridazine derivs. as ligands for GABA receptors*. WO 9937646.

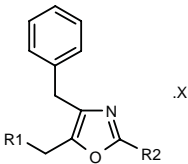
279733

1-(4-Benzyl-2-cyclohexyloxazol-5-ylmethyl)-4-(2-methoxyphenyl)piperidine fumarate



C29 H36 N2 O2 . C4 H4 O4; Mol wt: -0.4103

ACTION – A potent 5-HT_{1A} receptor agonist ($K_i = 4.4$ nM against [³H]-8-OH-DPAT binding in CHO cells transfected with the human 5-HT_{1A} receptor) with potential utility in the treatment of anxiety, depression, psychosis, Alzheimer’s disease, cognitive disorders, dementia, sleep disorders, drug and alcohol abuse or panic disorders. Other specifically claimed compounds from this series of oxazole derivatives include the following:



Compound	R1	R2	X	Formula
279735	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl	cyclohexyl	fumarate	C ₂₈ H ₃₁ N ₃ O .C ₄ H ₄ O ₄
279737	4-(2-MeOPh)-1-Pip	t-Bu	HCl	C ₂₇ H ₃₄ N ₂ O ₂ .HCl
279739	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl	cyclohexyl-CH2	HCl	C ₂₉ H ₃₃ N ₃ O .HCl

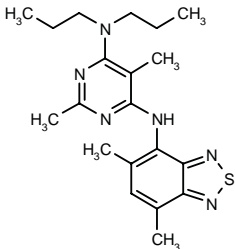
SOURCE – American Home Products.

REFERENCES

1. Kelly, M.G. et al. (American Home Products Corp.) *Oxazole derivs. as serotonin-1A receptor agonists*. WO 9938864.

279767

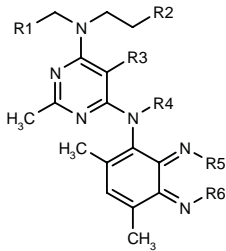
N⁴-(5,7-Dimethyl-2,1,3-benzothiadiazol-4-yl)-2,5-dimethyl-N⁶,N⁶-dipropylpyrimidine-4,6-diamine



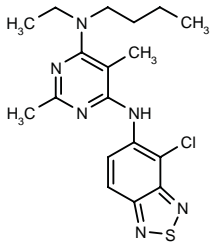
C20 H28 N6 S; Mol wt: 384.5492

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist with potential in the treatment of disease states mediated by CRF or in which the hypothalamic–pituitary axis (HPA) is dysregulated including inflammatory disorders such as arthritis, asthma and allergies, anxiety, phobic and panic attacks, depression, fatigue syndrome,

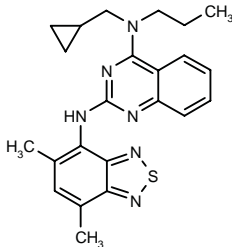
headache, pain, cancer, irritable bowel syndrome, immune dysfunction, HIV infection, neurodegenerative diseases, stroke, head trauma, epilepsy, eating disorders and sleep disorders. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
279768	Et	Me	Me	H	-O-		C ₂₀ H ₂₆ N ₆ O
279769	Et	Me	Me	H	-CH=CH-		C ₂₂ H ₃₀ N ₆
279771	Me	Et	-C(Me)=C(Me)-		-S-		C ₂₃ H ₃₀ N ₆ S
281864	cyclopropyl	Me	Me	H	-S-		C ₂₁ H ₂₈ N ₆ S



279770: C18 H23 Cl N6 S



279772: C23 H26 N6 S

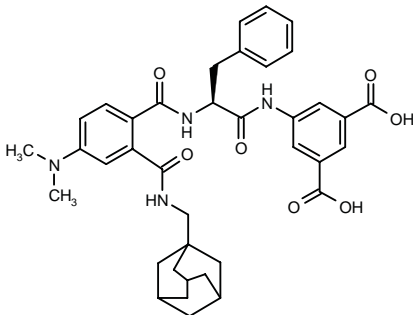
SOURCE – Novartis.

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1. Neumann, B.P. (Novartis AG) *Benzothiadiazoles and derivs*. WO 9940089.

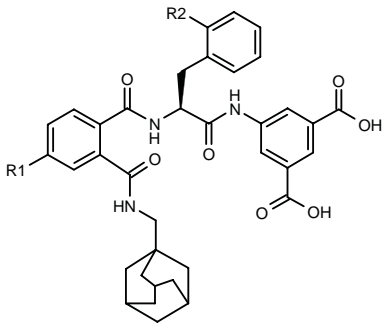
280242

5-[2(S)-[2-[N-(1-Adamantylmethyl)carbamoyl]-4-(dimethylamino)benzamido]-3-phenylpropionamido]benzene-1,3-dicarboxylic acid



C38 H42 N4 O7; Mol wt: 666.7708

ACTION – Cholecystokinin (CCK) and gastrin receptor antagonist with potent binding affinity for CCK₂ (CCK_B) receptors (pK_i = 8.8 in mouse cortical membranes) and potent gastrin-antagonist activity (pK_B = 8.6 for inhibition of pentagastrin-stimulated acid secretion in immature rat stomach). Potentially useful in the treatment of CNS, gastrointestinal and eating disorders and pain. Other exemplified compounds include the following:



Compound	R1	R2	Formula
280243	H	H	C ₃₆ H ₃₇ N ₃ O ₇
280244	NHMe	H	C ₃₇ H ₄₀ N ₄ O ₇
280245	OMe	F	C ₃₇ H ₃₈ FN ₃ O ₈

SOURCE – James Black Foundation.

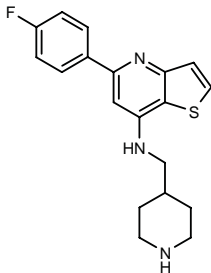
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280371

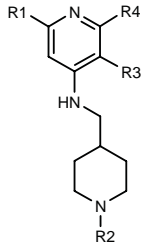
5-(4-Fluorophenyl)-N-(4-piperidinylmethyl)thieno[3,2-*b*]pyridin-7-amine

N-[5-(4-Fluorophenyl)thieno[3,2-*b*]pyridin-7-yl]-N-(4-piperidinylmethyl)amine



C19 H20 F N3 S; Mol wt: 341.4520

ACTION – Agent for the treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for the enhancement of memory with high affinity for the benzodiazepine binding site on the GABA_A receptor complex. Other specifically claimed compounds from this series of 4-(4-piperidylmethylamino) substituted pyridines include the following:



Compound	R1	R2	R3	R4	Formula
280372	Ph	H	-SCH=CH-		C ₁₉ H ₂₁ N ₃ S
280373	4-MeO-Ph	H	-SCH=CH-		C ₂₀ H ₂₃ N ₃ OS
280374	4-EtO-Ph	H	-SCH=CH-		C ₂₁ H ₂₅ N ₃ OS
280375	4-Pyr	H	-SCH=CH-		C ₁₈ H ₂₀ N ₄ S
280376	4-F-Ph	CONHEt	-SCH=CH-		C ₂₂ H ₂₅ FN ₄ OS
280377	H	H	-N=C(Ph)CH=CH-		C ₂₀ H ₂₂ N ₄
280378	Ph	H	-CH=CHS-		C ₁₉ H ₂₁ N ₃ S

SOURCE – Neurogen.

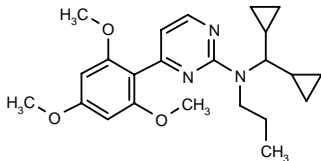
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1. Cai, G. and Liu, G. (Neurogen Corp.) *4-(4-Piperidylmethylamino) subst. heteroaryl fused pyridines: GABA brain receptor ligands*. WO 9943681.

NBI-27155*

246832

N-(Dicyclopropylmethyl)-N-propyl-N-[4-(2,4,6-trimethoxyphenyl)pyrimidin-2-yl]amine



C23 H31 N3 O3; Mol wt: 397.5220

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist proven to block ACTH release *in vivo*. Potentially useful for the treatment of depression and anxiety-related disorders.

SOURCE – Neurocrine Biosciences.

REFERENCES

1. McCarthy, J.R. et al. (Neurocrine Biosciences Inc.) *Amino-subst. thiadiazoles, pyrimidines, triazines or triazoles useful as CTF receptor antagonists*. EP 846108, JP 99507358, US 5795905, WO 9639400.

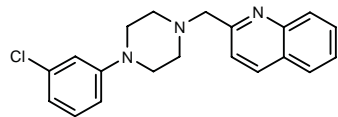
2. Chen, C. et al. *Design, synthesis, and SAR studies of 2-dialkylamino-4-arylpyrimidines as potent CRF receptor antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 110.

*Identified compound **246832** (see **245950**) Drug Data Rep 1997, 019(04): 0302.

ANTIPSYCHOTIC DRUGS

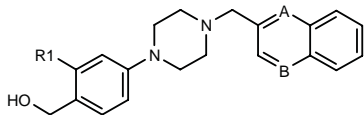
280379

2-[4-(3-Chlorophenyl)piperazin-1-ylmethyl]quinoline



C20 H20 Cl N3; Mol wt: 337.8520

ACTION – Potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding assays by K_i values of 2.72 and > 5882 nM for D₄ and D₂ receptors, respectively. Potentially useful for the treatment of psychosis and schizophrenia. Other compounds from this series of quinoliny derivatives include the following:



Compound	R1	A	B	Formula
280380	Cl	N	CH	C ₂₁ H ₂₂ ClN ₃ O
280381	F	CH	N	C ₂₁ H ₂₂ FN ₃ O
280382	Br	CH	N	C ₂₁ H ₂₂ BrN ₃ O

SOURCE – Warner-Lambert.

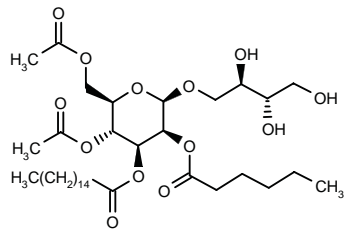
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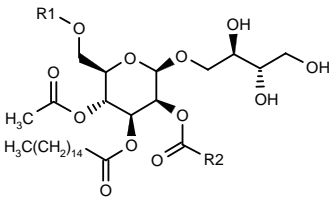
279610

4,6-*O*-Diacetyl-3-*O*-hexadecanoyl-2-*O*-hexanoyl-1-*O*-[2(*R*),3(*S*),4-trihydroxybutyl]-β-*D*-mannopyranose



C36 H64 O13; Mol wt: 704.8886

ACTION – Agent for the treatment of schizophrenia or diseases caused by dopamine metabolic dysfunction, produced by the microorganism *Ustilago maydis* FH 2634 (DSM 11494) and possessing dopamine D₃ and D₂ receptor-antagonist activity (IC₅₀ = 5 and 30 μg/ml, respectively). Compound is devoid of hemolytic properties, as demonstrated in human erythrocytes. Other compounds isolated from the same source are:



Compound	R1	R2	Formula
Ustilipid C [279611]	H	i-Pr	C ₃₂ H ₅₈ O ₁₂
Ustilipid B [279612]	Ac	Pr	C ₃₄ H ₆₀ O ₁₃

SOURCE – Hoechst Marion Roussel.

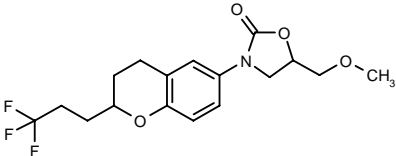
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1. Vértessy, L. et al. (Hoechst Marion Roussel Deutschland GmbH) *Ustilipides, method for the production and the use thereof*. DE 19802450, WO 9937658.

TREATMENT OF MOOD DISORDERS

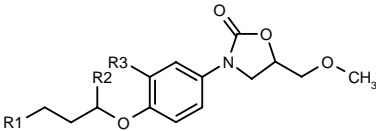
278888

5-(Methoxymethyl)-3-[2-(3,3,3-trifluoropropyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl]oxazolidin-2-one



C17 H20 F3 N O4; Mol wt: 359.3420

ACTION – Potent and selective inhibitor of monoamine oxidase type A (MAO-A) with potential in the treatment of depression, panic attacks, anxiety and cognitive impairment, as well as in the treatment or prevention of neurodegenerative disorders, alcohol and tobacco addiction and appetite loss. Other specifically claimed compounds within this series of oxazolidin-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
278889	H	-CH2CH2-		C ₁₇ H ₂₃ NO ₄
278891	CF3	-CH2-		C ₁₈ H ₁₈ F ₃ NO ₄

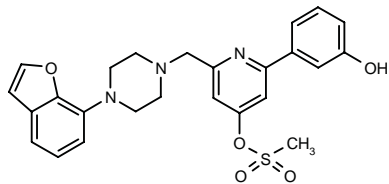
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Jegham, S. et al. (Synthélabo) *Cpds. derived from oxazolidin-2-one and preparation and therapeutical use thereof*. US 5925662, WO 9717347.

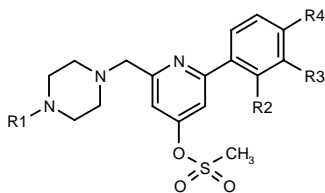
279132

Methanesulfonic acid 2-[4-(benzofuran-7-yl)piperazin-1-ylmethyl]-6-(3-hydroxyphenyl)pyridin-4-yl ester



C25 H25 N3 O5 S; Mol wt: 479.5545

ACTION – Agent for the treatment of CNS disorders with high affinity for 5-HT₇ receptors (K_i = 9.2 nM against [³H]-5-HT binding to cloned human 5-HT₇ receptors expressed in HEK 293 cells). Within this series of pyridine derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
279133	7-benzofuryl	OH	H	H	C ₂₅ H ₂₅ N ₃ O ₅ S
279134	2-OH-Ph	H	CONH2	H	C ₂₄ H ₂₆ N ₄ O ₅ S
279135	7-benzofuryl	OMe	H	H	C ₂₆ H ₂₇ N ₃ O ₅ S
279136	7-benzofuryl	H	-OCH2O-	H	C ₂₆ H ₂₅ N ₃ O ₆ S
279137	2-OH-Ph	H	OH	H	C ₂₃ H ₂₅ N ₃ O ₅ S
279138	2-MeO-Ph	H	OH	H	C ₂₄ H ₂₇ N ₃ O ₅ S

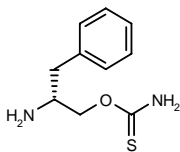
SOURCE – Shionogi.

REFERENCES

1. Adachi, M. et al. (Shionogi & Co. Ltd.) *Novel pyridine cpds.* WO 9931062.

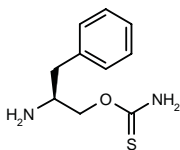
280238

Thiocarbamic acid *O*-[2(*R*)-amino-3-phenylpropyl] ester



C10 H14 N2 O S; Mol wt: 210.2996

ACTION – Agent for the treatment of CNS disorders, particularly anxiety and depression, a representative compound from a series of *O*-thiocarbamoyl-aminoalkanol derivatives. Antidepressant activity was demonstrated in the forced swimming test in mice (41.6% inhibition at 30 mg/kg i.p.), and anticonvulsant effects were shown in the maximal electroshock (MES) test in mice (ED_{50} = 29.0 mg/kg i.p. and 188.8 mg/kg p.o.). Another specifically claimed compound is:



280239: C10 H14 N2 O S

SOURCE – SK Corp.

REFERENCES

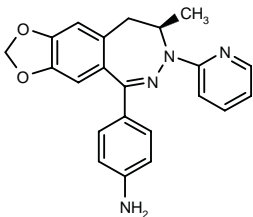
1. Choi, Y.M. and Kim, Y.K. (SK Corporation) *O*-Thiocarbamoyl-aminoalkanol cpds., their pharmaceutically useful salts and process for preparing the same. US 5935997.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

278859

5-(4-Aminophenyl)-8(*R*)-methyl-7-(2-pyridinyl)-8,9-dihydro-7*H*-1,3-dioxolo[4,5-*h*]-2,3-benzodiazepine



C22 H20 N4 O2; Mol wt: 372.4260

ACTION – Anticonvulsant, an AMPA receptor antagonist proven to protect mice from seizures induced by maximal electroshock (MES model) with activity similar to that of the clinical candidate AMPA antagonist talampanel (LY-300164; ED_{50} = 0.76 and 0.48 mg/kg i.v., respectively). Compound at 10 μ M blocked (by 50% or more) AMPA-induced depolarization in rat cortical wedges.

SOURCE – Lilly.

REFERENCES

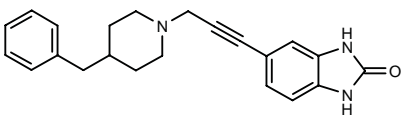
1. Anderson, B.A. et al. (Eli Lilly and Company) *Physical form of dihydro-2,3-benzodiazepine deriv.* EP 699676, JP 96081468, JP 96081469, JP 96092255, JP 98505066, US 5795886.

2. Anderson, B.A. et al. *Synthesis and anticonvulsant activity of 3-aryl-5*H*-2,3-benzodiazepine AMPA antagonists.* Bioorg Med Chem Lett 1999, 9(14): 1953.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

279803

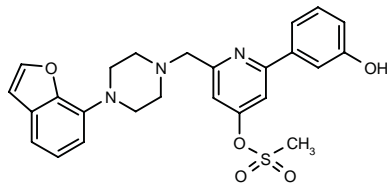
5-[3-(4-Benzylpiperidin-1-yl)-1-propynyl]-2,3-dihydro-1*H*-benzimidazol-2-one



C22 H23 N3 O; Mol wt: 345.4437

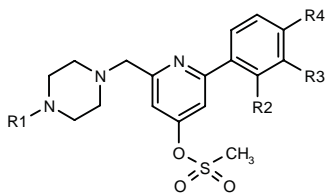
279132

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C25 H25 N3 O5 S; Mol wt: 479.5545

ACTION – Agent for the treatment of CNS disorders with high affinity for 5-HT₇ receptors (K_i = 9.2 nM against [³H]-5-HT binding to cloned human 5-HT₇ receptors expressed in HEK 293 cells). Within this series of pyridine derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
279133	7-benzofuryl	OH	H	H	C ₂₅ H ₂₅ N ₃ O ₅ S
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279135	7-benzofuryl	OMe	H	H	C ₂₆ H ₂₇ N ₃ O ₅ S
279136	7-benzofuryl	H	-OCH2O-	H	C ₂₆ H ₂₅ N ₃ O ₆ S
279137	2-OH-Ph	H	OH	H	C ₂₃ H ₂₅ N ₃ O ₅ S
279138	2-MeO-Ph	H	OH	H	C ₂₄ H ₂₇ N ₃ O ₅ S

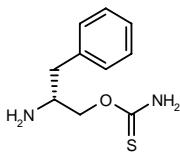
SOURCE – Shionogi.

REFERENCES

1. Adachi, M. et al. (Shionogi & Co. Ltd.) *Novel pyridine cpds.* WO 9931062.

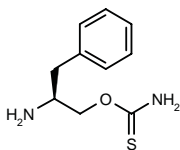
280238

Thiocarbamic acid O-[2(R)-amino-3-phenylpropyl] ester



C10 H14 N2 O S; Mol wt: 210.2996

ACTION – Agent for the treatment of CNS disorders, particularly anxiety and depression, a representative compound from a series of O-thiocarbamoyl-aminoalkanol derivatives. Antidepressant activity was demonstrated in the forced swimming test in mice (41.6% inhibition at 30 mg/kg i.p.), and anticonvulsant effects were shown in the maximal electroshock (MES) test in mice (ED_{50} = 29.0 mg/kg i.p. and 188.8 mg/kg p.o.). Another specifically claimed compound is:



280239: C10 H14 N2 O S

SOURCE – SK Corp.

REFERENCES

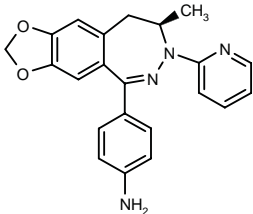
1. Choi, Y.M. and Kim, Y.K. (SK Corporation) *O-Thiocarbamoyl-aminoalkanol cpds., their pharmaceutically useful salts and process for preparing the same.* US 5935997.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

278859

5-(4-Aminophenyl)-8(R)-methyl-7-(2-pyridinyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h]-2,3-benzodiazepine



C22 H20 N4 O2; Mol wt: 372.4260

ACTION – Anticonvulsant, an AMPA receptor antagonist proven to protect mice from seizures induced by maximal electroshock (MES model) with activity similar to that of the clinical candidate AMPA antagonist talampanel (LY-300164; ED_{50} = 0.76 and 0.48 mg/kg i.v., respectively). Compound at 10 μ M blocked (by 50% or more) AMPA-induced depolarization in rat cortical wedges.

SOURCE – Lilly.

REFERENCES

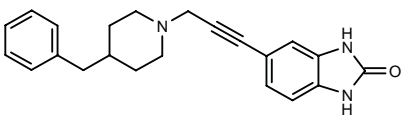
1. Anderson, B.A. et al. (Eli Lilly and Company) *Physical form of dihydro-2,3-benzodiazepine deriv.* EP 699676, JP 96081468, JP 96081469, JP 96092255, JP 98505066, US 5795886.

2. Anderson, B.A. et al. *Synthesis and anticonvulsant activity of 3-aryl-5H-2,3-benzodiazepine AMPA antagonists.* Bioorg Med Chem Lett 1999, 9(14): 1953.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

279803

5-[3-(4-Benzylpiperidin-1-yl)-1-propynyl]-2,3-dihydro-1H-benzimidazol-2-one



C22 H23 N3 O; Mol wt: 345.4437

ACTION – Potent NMDA receptor antagonist with high selectivity for the NR1A/2B subunit (IC_{50} = 7 nM) over the NR1A/2A and NR1A/2C subunits (IC_{50} = 25 and 72 μ M, respectively). Compound was shown to be active in an *in vivo* model of Parkinson’s disease.

SOURCES – CoCensys; Warner-Lambert.

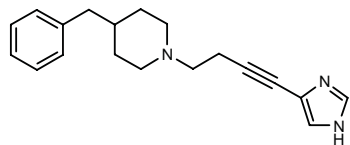
REFERENCES

1. Boxer, P.A. et al. *Synthesis and SAR of 4-benzyl piperidiny alkynyl heterocycles as subtype selective NMDA receptor antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 93.

PD-188669

279531

4-Benzyl-1-[4-(4-imidazolyl)-3-butynyl]piperidine



C19 H23 N3; Mol wt: 293.4117

ACTION – Potent NMDA receptor antagonist with high selectivity for NR1A/2B over NR1A/2A and NR1A/2C subtypes (IC_{50} = 0.37, 53 and 70 μ M, respectively). *In vivo*, compound (3 mg/kg p.o.) was able to potentiate the L-DOPA-induced contralateral rotations in 6-OHDA-lesioned rats. Potentially useful as add-on therapy to L-DOPA for the treatment of Parkinson’s disease.

SOURCES – Warner-Lambert; CoCensys.

REFERENCES

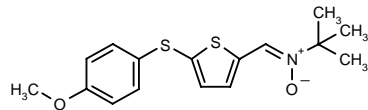
1. Bigge, C.F. et al. (Warner-Lambert Co.;CoCensys, Inc.) *4-Substd. piperidine analogs and their use as subtype selective NMDA receptor antagonists*. EP 869791, WO 9723214.
2. Gregory, T.F. et al. *Novel series of 4-benzyl-N-(4-imidazole-1-alkynyl)piperidines as potent subtype selective NMDA receptor antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 94.
3. Wright, J.L. et al. *Discovery of subtype-selective NMDA receptor ligands: 4-Benzyl-1-piperidinyalkynylpyrroles, pyrazoles and imidazoles as NR1A/2B antagonists*. Bioorg Med Chem Lett 1999, 9(19): 2815.

COGNITION-ENHANCING DRUGS

279013

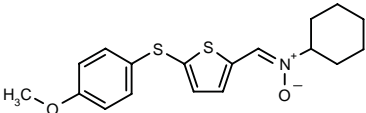
N-tert-Butyl-*N*-[5-(4-methoxyphenylsulfanyl)thiophen-2-ylmetylen]amine *N*-oxide

N-tert-Butyl- α -[5-(4-methoxyphenylsulfanyl)thiophen-2-yl]nitron



C16 H19 N O2 S2; Mol wt: 321.4631

ACTION – Agent for the treatment of neurodegenerative, autoimmune and inflammatory disorders, particularly Alzheimer’s disease, that acts by inhibiting the formation of A β (1-42) β -pleated sheets or the release of cytokines such as IL-1 β , as demonstrated in several *in vitro* assays. In addition, compound has free radical-scavenging activity. Another specifically claimed compound from this series of thiophene nitrones is:



279014: C18 H21 N O2 S2

SOURCE – Centaur.

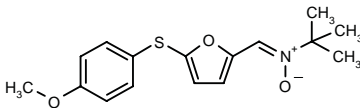
REFERENCES

1. Kelleher, J.A. et al. (Centaur Pharmaceuticals, Inc.) *Thiophene nitron cpds*. WO 9936420.

279040

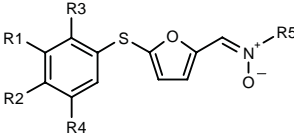
N-tert-Butyl-*N*-[5-(4-methoxyphenylsulfanyl)furan-2-yl-methylen]amine *N*-oxide

N-tert-Butyl- α -[5-(4-methoxyphenylsulfanyl)furan-2-yl]-nitron



C16 H19 N O3 S; Mol wt: 305.3961

ACTION – Agent for the treatment of neurodegenerative, autoimmune and inflammatory disorders, particularly Alzheimer’s disease, that acts by inhibiting the formation of A β (1-42) β -pleated sheets or the release of cytokines such as IL-1 β , as demonstrated in several *in vitro* assays. In addition, compound has free radical-scavenging activity. Other specifically claimed compounds from this series of thioether furan nitrones include the following:



Compound	R1	R2	R3	R4	R5	Formula
279041	H	H	OMe	H	t-Bu	C ₁₆ H ₁₉ NO ₃ S
279042	H	OMe	H	H	cyclohexyl	C ₁₈ H ₂₁ NO ₃ S
279043	H	OCF ₃	H	H	t-Bu	C ₁₆ H ₁₆ F ₃ NO ₃ S
279044	Me	H	H	Me	t-Bu	C ₁₇ H ₂₁ NO ₂ S
279045	H	NHAc	H	H	t-Bu	C ₁₇ H ₂₀ N ₂ O ₃ S
279046	H	Et	H	H	t-Bu	C ₁₇ H ₂₁ NO ₂ S
279047	H	OCH ₂ SH	H	H	t-Bu	C ₁₆ H ₁₉ NO ₃ S ₂
279048	H	OMe	H	H	i-Pr	C ₁₅ H ₁₇ NO ₃ S
279049	H	OCF ₃	H	H	cyclohexyl	C ₁₈ H ₁₈ F ₃ NO ₃ S
279050	H	OMe	H	H	Bu	C ₁₆ H ₁₉ NO ₃ S
279051	H	OMe	H	H	Pr	C ₁₅ H ₁₇ NO ₃ S
279052	H	OCF ₃	H	H	i-Pr	C ₁₅ H ₁₄ F ₃ NO ₃ S
279053	H	OCF ₃	H	H	Pr	C ₁₅ H ₁₄ F ₃ NO ₃ S
279054	H	OMe	H	H	t-BuCH ₂ C(Me) ₂	C ₂₀ H ₂₇ NO ₃ S
279055	H	OCF ₃	H	H	t-BuCH ₂ C(Me) ₂	C ₂₀ H ₂₄ F ₃ NO ₃ S
279056	H	OMe	H	H	cyclopentyl	C ₁₇ H ₁₉ NO ₃ S
279057	H	OCF ₃	H	H	cyclopentyl	C ₁₇ H ₁₆ F ₃ NO ₃ S

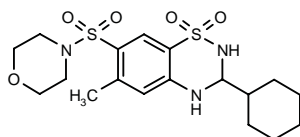
SOURCE – Centaur.

REFERENCES

1. Kelleher, J.A. et al. (Centaur Pharmaceuticals, Inc.) *Thioether furan nitron cpds.* WO 9936415.

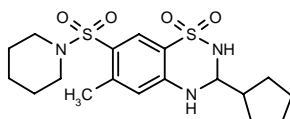
280359

3-Cyclohexyl-6-methyl-7-(4-morpholinylsulfonyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide



C18 H27 N3 O5 S2; Mol wt: 429.5593

ACTION – AMPA receptor agonist with an IC_{50} value of 7.0 μ M against [3 H]-AMPA binding in rat cortical homogenates. *In vitro*, compound was shown to concentration-dependently potentiate AMPA-induced [3 H]-GABA release from cultured cortical neurons and was active in voltage clamp experiments in mouse neocortical neurons, potentiating the current induced by application of 30 μ M AMPA. *In vivo*, it enhanced AMPA-induced spike activity in hippocampus when given to rats at 10 mg/kg i.v. Potentially useful for the treatment of memory disorders, psychosis, sexual dysfunction, schizophrenia, depression, Alzheimer's disease, trauma, stroke and epilepsy. Within this series of bicyclic compounds, the following is also included:



280360: C19 H29 N3 O4 S2

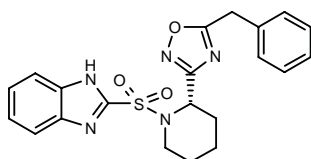
SOURCE – NeuroSearch.

REFERENCES

1. Goulliaev, A.H. et al. (NeuroSearch A/S) *Novel cpds. and their use as positive AMPA receptor modulators.* WO 9942456.

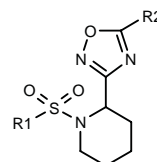
281190

2-[2(S)-(5-Benzyl-1,2,4-oxadiazol-3-yl)piperidin-1-yl-sulfonyl]-1H-benzimidazole



C21 H21 N5 O3 S; Mol wt: 423.4949

ACTION – Rotamase inhibitor with affinity for the FK-506-binding protein (FKBP)-type immunophilins that acts as a neurotrophic agent while lacking significant immunosuppressive activity. Expected to be particularly useful for the treatment of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other motor neuron diseases, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, physical or traumatic damage to the central or peripheral nervous system, peripheral neuropathy, multiple sclerosis or hearing disorders such as tinnitus. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Isomer	Formula
281191	2-benzimidazolyl	4-(1-pyrrolidinyl-CH2)-PhOCH2		C ₂₆ H ₃₀ N ₆ O ₄ S
281192	cyclohexyl-CH2	N(Me)Ph	S	C ₂₁ H ₃₀ N ₄ O ₃ S
281193	2-benzimidazolyl	4-Pip-OCH2	S	C ₂₀ H ₂₆ N ₆ O ₄ S
281194	cyclohexyl-CH2	4-(t-Bu-OCO)-1-Piz-CH2CH2	S	C ₂₅ H ₄₃ N ₅ O ₅ S
281196	cyclopentyl-CH2	CH2Ph	S	C ₂₀ H ₂₇ N ₃ O ₃ S
281197	4-F-Ph	4-(CH2OH)-PhOCH2	S	C ₂₁ H ₂₂ FN ₃ O ₅ S

SOURCE – Pfizer.

REFERENCES

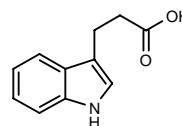
1. Bull, D.J. et al. (Pfizer Inc.;Pfizer Ltd.) *Heterocyclic cpds. as inhibitors of rotamase enzymes.* WO 9945006.

INDOLE-3-PROPIONIC ACID

280233

3-(1H-Indol-3-yl)propionic acid

IPA



C11 H11 N O2; Mol wt: 189.2129

ACTION – Neuroprotective agent, a radical scavenger that is able to completely protect primary neurons and neuroblastoma cells from oxidative damage and cell death caused by exposure to amyloid β -protein. The antioxidant activity of the compound is superior to that of melatonin, the most potent naturally occurring free radical scavenger. Found in plasma and cerebrospinal fluid under physiological conditions, the compound does not generate prooxidant intermediates and is not cytotoxic. Potentially useful for the treatment of Alzheimer's disease and disorders in which free radicals may be implicated.

SOURCES – University of Louisville, Louisville, KY (US); New York University, New York, NY (US); University of South Alabama, Mobile, AL (US).

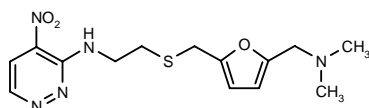
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2. Chyan, Y.J. et al. *Potent neuroprotective properties against the Alzheimer β -amyloid by an endogenous melatonin-related indole structure, indole-3-propionic acid*. J Biol Chem 1999, 274(31): 21937.

JWS-USC-75IX

222591

N-[2-[5-(Dimethylaminomethyl)-2-furylmethylsulfanyl]-ethyl]-4-nitropyridazin-3-amine



C14 H19 N5 O3 S; Mol wt: 337.4021

ACTION – Cognition-enhancing agent, a ranitidine analogue that acts as a potent and selective muscarinic M_2 receptor antagonist (IC_{50} = 0.060 and 0.97, respectively, for M_2 and M_1 receptors in binding assays) and acetylcholinesterase (AChE) inhibitor (IC_{50} = 0.47 and 10 μ M, respectively, against AChE and butyrylcholinesterase), with low affinity for nicotinic acetylcholine receptors (K_i = 370 μ M). Compound significantly improved scopolamine-induced learning deficits in a rat passive avoidance test (1 mg/kg i.p.) and it improved learning in the Morris water maze in rats (0.1-1 mg/kg i.p.).

SOURCES – University of Georgia, Athens, GA (US); University of South Carolina, Columbia, SC (US).

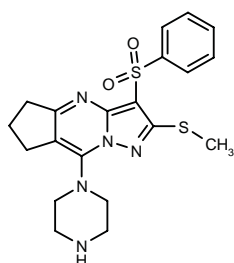
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1. Terry, A.V. Jr. et al. *Enhanced performance of a rat stimulus discrimination task following administration of JWS USC 75IX, a novel ranitidine analog*. FASEB J 1995, 9(3, Part 1): Abst 2227.
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3. Terry, A.V. Jr. et al. *Ranitidine analog, JWS-USC-75IX, enhances memory-related task performance in rats*. Drug Dev Res 1999, 47(2): 97.
4. Valli, M.J. et al. *Synthesis and cholinergic properties of N-aryl-2-[[5-[(dimethylamino)methyl]-2-furyl]methyl]thio]ethylamino analogs of ranitidine*. J Med Chem 1992, 35(17): 3141.

RO-65-7674

279672

2-(Methylsulfanyl)-3-(phenylsulfonyl)-8-(piperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine



C20 H23 N5 O2 S2; Mol wt: 429.5667

ACTION – Potent 5-HT₆ receptor antagonist (pK_i = 9.07) with high selectivity over a number of other binding sites, proven to increase extracellular acetylcholine content in the frontal cortex of freely moving rats at a dose of 30 mg/kg p.o., as well as to reverse scopolamine-induced memory deficits in animal models of cognitive function. Potential clinical candidate for the treatment of memory impairment in Alzheimer's disease patients.

SOURCE – Roche.

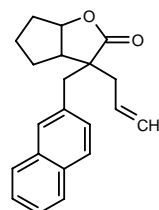
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2. Stadler, H. et al. *5HT₆ antagonists: A novel approach for the symptomatic treatment of Alzheimer's disease*. 37th IUPAC Congr (Aug 14-19, Berlin) 1999, Abst MM-7.

TREATMENT OF
CEREBROVASCULAR DISEASES

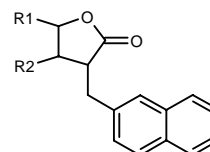
278999

3-Allyl-3-(2-naphthylmethyl)perhydrocyclopenta[b]furan-2-one



C21 H22 O2; Mol wt: 306.4028

ACTION – Metabotropic glutamate mglu1 receptor antagonist with potential in the treatment or prevention of cerebral ischemia, cranial/cerebral trauma, pain and CNS-mediated cramps. Other specifically claimed compounds from this series of substituted β,γ -anellated lactones include the following:



Compound	R1	R2	Formula
279000	-CH ₂ CH=CH-		C ₁₈ H ₁₆ O ₂
279001	-CH=CHCH ₂ -		C ₁₈ H ₁₆ O ₂

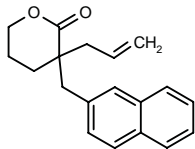
SOURCE – Bayer.

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1. Stolle, A. et al. (Bayer AG) *Substd. β,γ -anellated lactones*. DE 19801647, WO 9936417.

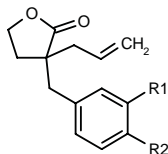
279002

3-Allyl-3-(2-naphthylmethyl)tetrahydropyran-2-one



C19 H20 O2; Mol wt: 280.3650

ACTION – Metabotropic glutamate receptor modulator with potential in the treatment of diseases caused by the hyper- or hypofunction of the glutamatergic system, especially cerebral ischemia, cranial/cerebral trauma and pain. Other specifically claimed compounds from this series of substituted lactones include the following:



Compound	R1	R2	Formula
279003	H	H	C ₁₄ H ₁₆ O ₂
279004	-CH=CHCH=CH-		C ₁₈ H ₁₈ O ₂
279005	-OCH2O-		C ₁₅ H ₁₆ O ₄
279006	-CH=CHC(t-Bu)=CH-		C ₂₂ H ₂₆ O ₂

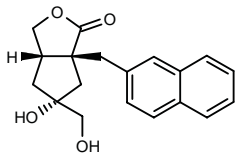
SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer AG) *Substd. lactones as modulators of metabotropic glutamate receptors*. DE 19801648, WO 9936419.

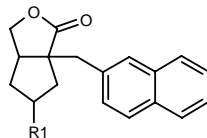
279007

(3a*S**,5*R**,6a*R**)-5-Hydroxy-5-(hydroxymethyl)-6a-(2-naphthylmethyl)perhydrocyclopenta[*c*]furan-1-one



C19 H20 O4; Mol wt: 312.3630

ACTION – Metabotropic glutamate receptor subtype 1 (mglu1) antagonist with potential in the treatment or prevention of cerebral ischemia, cranial/cerebral trauma and pain. Other specifically claimed compounds from this series of substituted bicyclic lactones include the following:



Compound	R1	Formula
279008	H	C ₁₈ H ₁₈ O ₂
279009	OMe	C ₁₉ H ₂₀ O ₃
279010	Me	C ₁₉ H ₂₀ O ₂

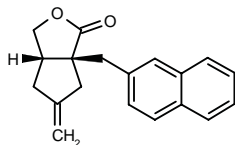
SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer AG) *Substd. bicyclic lactones*. DE 19801636, WO 9936418.

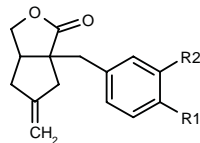
279058

(3a*S*,6a*S*)-5-Methylene-6a-(2-naphthylmethyl)perhydrocyclopenta[*c*]furan-1-one

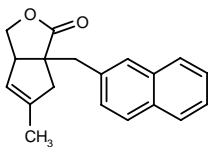


C19 H18 O2; Mol wt: 278.3492

ACTION – Metabotropic glutamate receptor modulator with potential in the treatment of diseases caused by hyper- or hypofunction of the glutamatergic system, especially cerebral ischemia, cranial/cerebral trauma and pain. In a rat model of permanent focal cerebral ischemia, compound produced a 38% reduction in infarct volume when given as an i.v. infusion at 0.01 mg/kg/h. In addition, it was active in a rat model of subdural hematoma, giving 51% reduction of infarct volume at a dose of 0.01 mg/kg/h i.v. Other specifically claimed compounds from this series of substituted α,β -anellated butyrolactones include the following:



Compound	R1	R2	Isomer	Formula
279059	NHCOCH2Ph	H	3a <i>S</i> ,6a <i>S</i>	C ₂₃ H ₂₃ NO ₃
279060	cyclopentyl-CH2CH2CONH	H	3a <i>S</i> ,6a <i>S</i>	C ₂₃ H ₂₉ NO ₃
279061	3-thienyl-CH2CONH	H		C ₂₁ H ₂₁ NO ₃ S
279062	NHCO2Pr	H	3a <i>S</i> ,6a <i>S</i>	C ₁₉ H ₂₃ NO ₄
279063	3-OH-PhCH2CONH	H	3a <i>S</i> ,6a <i>S</i>	C ₂₃ H ₂₃ NO ₄
279064	CONHC7H15	H		C ₂₃ H ₃₁ NO ₃
279065	allyl-OCONH	H	3a <i>S</i> ,6a <i>S</i>	C ₁₉ H ₂₁ NO ₄
279066	4-Me-PhCH2CH2NHCO	H	3a <i>S</i> ,6a <i>S</i>	C ₂₆ H ₂₇ NO ₃
279067	OMe	Br	3a <i>S</i> ,6a <i>S</i>	C ₁₆ H ₁₇ BrO ₃
279068	3-MeO-PhCH2CONH	H	3a <i>S</i> ,6a <i>S</i>	C ₂₄ H ₂₅ NO ₄



279069: C19 H18 O2

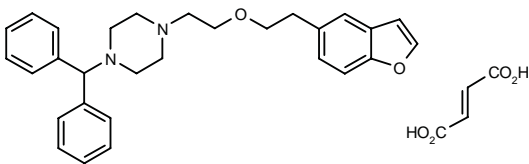
SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer AG) *Substd. α,β-anellated butyrolactones*. DE 19801646, WO 9936416.

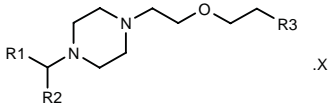
279150

1-Benzhydryl-4-[2-[2-(1-benzofuran-5-yl)ethoxy]ethyl]-piperazine fumarate

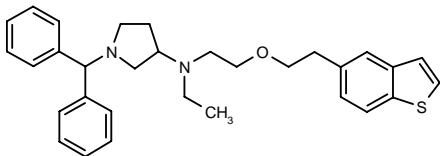


C29 H32 N2 O2 . C4 H4 O4; Mol wt: 556.6554

ACTION – Calcium channel blocker, as demonstrated by 100% inhibition of calcium uptake in rat cerebral cortex synaptosome preparations at 10 μM. A representative compound from a series of alkyl ether derivatives, wherein the following are also included:



Compound	R1	R2	R3	X	Formula
279151	H	4-Cl-Ph	2-Naph		C ₂₅ H ₂₉ ClN ₂ O
279153	Ph	Ph	2-Naph		C ₃₁ H ₃₄ N ₂ O
279154	Ph	Ph	5-benzothieryl	2HCl	C ₂₉ H ₃₂ N ₂ OS.2HCl
279155	Ph	Ph	6-F-5-benzothieryl		C ₂₉ H ₃₁ FN ₂ O ₂ S
279156	H	CH ₂ CH ₂ -CH(Ph) ₂	5-benzothieryl		C ₃₂ H ₃₈ N ₂ OS



279152: C31 H36 N2 O S

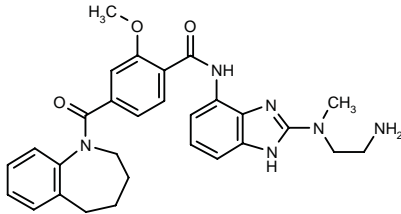
SOURCE – Toyama.

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1. Ono, S. et al. (Toyama Chemical Co., Ltd.) *Alkyl ether derivs. or salts thereof and calcium antagonists containing the same*. JP 99263773, WO 9931056.

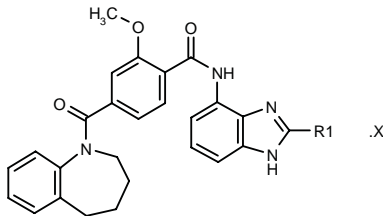
279552

N-[2-[*N*-(2-Aminoethyl)-*N*-methylamino]-1*H*-benzimidazol-4-yl]-2-methoxy-4-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-ylcarbonyl)benzamide



C29 H32 N6 O3; Mol wt: 512.6108

ACTION – Vasopressin antagonist with selectivity for V₁ receptors (IC₅₀ = 0.08 nM against [³H]-vasopressin binding in human platelet preparations) relative to V₂ receptors (IC₅₀ = 140 nM against [³H]-vasopressin binding in CHO cells expressing the human V₂ receptor), potentially useful in the treatment or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, hepatocirrhosis, hyponatremia, hypokalemia, circulation disorders, and particularly cerebrovascular disorders, depression, anxiety and the like. Within this series of benzamide derivatives, the following are also included:



Compound	R1	X	Formula
279553	Me		C ₂₇ H ₂₆ N ₄ O ₃
279554	H	HCl	C ₂₆ H ₂₄ N ₄ O ₃ .HCl
279555	Et	HCl	C ₂₈ H ₂₈ N ₄ O ₃ .HCl
279556	CON(Me) ₂		C ₂₉ H ₂₉ N ₅ O ₄

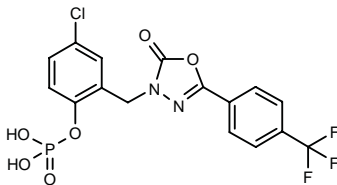
SOURCE – Fujisawa.

REFERENCES

1. Setoi, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Benzamide derivs. as vasopressin antagonists*. WO 9937637.

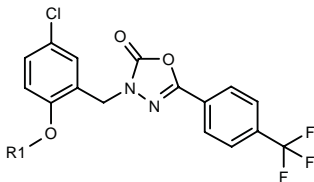
279584

Phosphoric acid 4-chloro-2-[2-oxo-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,3,4-oxadiazol-3-ylmethyl]phenyl monoester



C16 H11 Cl F3 N2 O6 P; Mol wt: 450.6919

ACTION – Agent for the treatment of ischemia, stroke, convulsions, epilepsy, asthma, irritable bowel syndrome, migraine, traumatic brain injury, spinal cord injury, sexual dysfunction and urinary incontinence that acts as an opener of large-conductance Ca²⁺-activated potassium channels (BK channels). Other exemplified compounds from this series of phosphate derivatives of diaryl 1,3,4-oxadiazolones include the following:



Compound	R1	Formula
279585	PO(OH)ONa	C ₁₆ H ₁₀ ClF ₃ N ₂ NaO ₆ P
279586	CH ₂ OPO ₃ H ₂	C ₁₇ H ₁₃ ClF ₃ N ₂ O ₇ P
279587	CO ₂ CH ₂ OPO ₃ H ₂	C ₁₈ H ₁₃ ClF ₃ N ₂ O ₈ P
279588	COCH ₂ OPO ₃ H ₂	C ₁₈ H ₁₃ ClF ₃ N ₂ O ₈ P

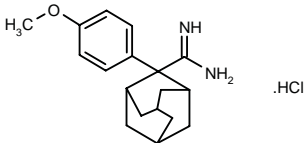
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Phosphate derivs. of diaryl 1,3,4-oxadiazolone*. US 5939405, WO 9938873.

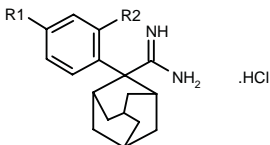
279667

2-(4-Methoxyphenyl)adamantane-2-carboxamidine hydrochloride



C₁₈ H₂₄ N₂ O . HCl; Mol wt: 320.8615

ACTION – NMDA receptor antagonist found to possess a favorable ratio of cortical (IC₅₀ = 45 μM) to cerebellar (IC₅₀ = 22 μM) binding affinity, which is expected to result in good *in vivo* tolerance. Potentially useful in the treatment of disorders associated with abnormal glutamatergic transmission such as stroke, traumatic brain injury and neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease. Other exemplified adamantane-carboximidamide derivatives are:



Compound	R1	R2	Formula
279668	Me	H	C ₁₈ H ₂₄ N ₂ .HCl
279669	H	Me	C ₁₈ H ₂₄ N ₂ .HCl
279670	F	H	C ₁₇ H ₂₁ FN ₂ .HCl
279671	Cl	H	C ₁₇ H ₂₁ ClN ₂ .HCl

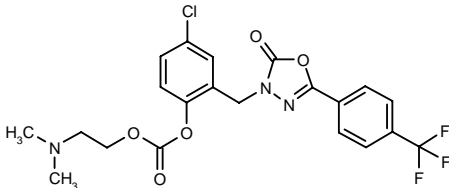
SOURCE – Cerebrus.

REFERENCES

1. Monck, N.J.T. et al. (Cerebrus Ltd.) *Adamantanecarboximidamide derivs. and their use as NMDA antagonists*. WO 9938841.

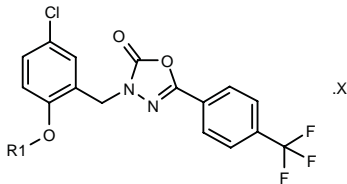
279690

Carbonic acid [4-chloro-2-[2-oxo-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,3,4-oxadiazol-3-ylmethyl]phenyl]-[2-(dimethylamino)ethyl] diester



C₂₁ H₁₉ Cl F₃ N₃ O₅; Mol wt: 485.8441

ACTION – Agent for the treatment of ischemia, stroke, convulsions, epilepsy, asthma, irritable bowel syndrome, migraine, traumatic brain injury, spinal cord injury, sexual dysfunction and urinary incontinence that acts as an opener of large-conductance Ca²⁺-activated potassium channels (BK channels). Other specifically claimed compounds from this series of 1,3,4-oxadiazolone derivatives include the following:



Compound	R1	X	Formula
279691	CO ₂ CH ₂ CH ₂ N(Me) ₃ ⁺	MeSO ₃ ⁻	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₈ S
279692	COCH ₂ N(Me) ₂		C ₂₀ H ₁₇ ClF ₃ N ₃ O ₄
279693	COCH ₂ CH ₂ N(Et) ₂	HCl	C ₂₃ H ₂₃ ClF ₃ N ₃ O ₄ .HCl
279694	CO(CH ₂) ₃ N(Me) ₂	HCl	C ₂₂ H ₂₁ ClF ₃ N ₃ O ₄ .HCl
279695	COCH ₂ N(Me) ₃ ⁺	MeSO ₃ ⁻	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₇ S
279696	COCH ₂ CH ₂ N(Et) ₂ Me ⁺	MeSO ₃ ⁻	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₇ S
279699	CO(CH ₂) ₃ N(Me) ₃ ⁺	MeSO ₃ ⁻	C ₂₄ H ₂₇ ClF ₃ N ₃ O ₇ S
279702	COCH ₂ CH ₂ NHMe		C ₂₀ H ₁₇ ClF ₃ N ₃ O ₄
279703	COCH ₂ CH ₂ NH ₂		C ₁₉ H ₁₅ ClF ₃ N ₃ O ₄
279704	CH ₂ OCO(CH ₂) ₃ N(Me) ₂		C ₂₃ H ₂₃ ClF ₃ N ₃ O ₅
279705	CH ₂ OCO(CH ₂) ₃ N(Me) ₃ ⁺	MeSO ₃ ⁻	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₈ S

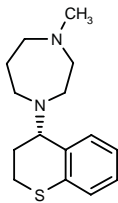
SOURCE – Bristol-Myers Squibb.

REFERENCES

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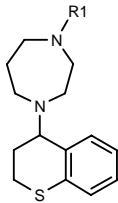
279724

(+)-1-[3,4-Dihydro-2*H*-benzo[*b*]thiopyran-4(*S*)-yl]-4-methylperhydro-1,4-diazepine



C15 H22 N2 S; Mol wt: 262.4188

ACTION – Neuroprotective agent with selective binding affinity for the [³H]-emopamil binding site; it does not act directly at either voltage-sensitive calcium channels (VSCC) or NMDA receptors, and thus exhibits fewer side effects than emopamil (hypotension) or ifenprodil (behavioral symptoms). Compound gave an IC₅₀ of 9 nM in a [³H]-emopamil binding assay using guinea pig liver membranes, whereas the value was about 15,000 nM for [³H]-D-888 binding to L-type VSCC in rat brain cortical membranes. Potentially useful in the treatment of neurological disorders such as stroke, head trauma, transient cerebral ischemic attack and chronic neurodegenerative disorders such as Alzheimer’s disease, vascular dementia, AIDS-related dementia, Parkinson’s disease, Huntington’s disease, diabetic neuropathy, amyotrophic lateral sclerosis and multiple sclerosis. Other specifically claimed compounds from this series of 1,4-diazacycloheptane derivatives include the following:



Compound	R1	Isomer	Formula
279725	H		C ₁₄ H ₂₀ N ₂ S
279726	i-Pr		C ₁₇ H ₂₆ N ₂ S
279727	H	S	C ₁₄ H ₂₀ N ₂ S
279728	Me		C ₁₅ H ₂₂ N ₂ S
279729	CH2Ph		C ₂₁ H ₂₆ N ₂ S
279730	i-Bu		C ₁₈ H ₂₈ N ₂ S
279731	i-BuCH2		C ₁₉ H ₃₀ N ₂ S
279732	Pr		C ₁₇ H ₂₆ N ₂ S

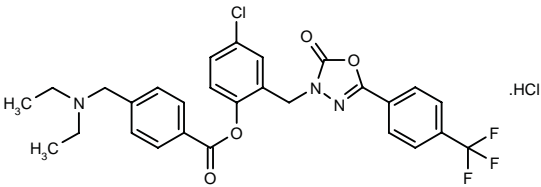
SOURCE – AstraZeneca.

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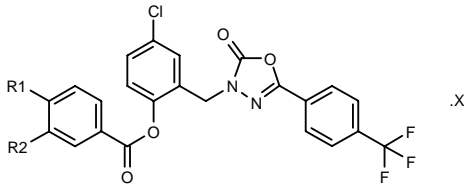
279807

4-(Diethylaminomethyl)benzoic acid 4-chloro-2-[2-oxo-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,3,4-oxadiazol-3-ylmethyl]phenyl ester hydrochloride



C28 H25 Cl F3 N3 O4 . HCl; Mol wt: 596.4304

ACTION – Agent for the treatment of ischemia, stroke, convulsions, epilepsy, asthma, irritable bowel syndrome, migraine, traumatic brain injury, sexual dysfunction and urinary incontinence, a prodrug of a known large-conductance Ca²⁺-activated potassium channel (BK_{Ca} channel) opener. Other compounds from this series of benzoate derivatives of diaryl 1,3,4-oxadiazolones include the following:



Compound	R1	R2	X	Formula
279809	4-morpholinyl-CH2	H	HCl	C ₂₈ H ₂₃ Cl ₂ F ₃ N ₃ O ₅ .HCl
279810	1-Pip-CH2	H	HCl	C ₂₉ H ₂₅ ClF ₃ N ₃ O ₄ .HCl
279811	4-Me-1-Piz-CH2	H	2HCl	C ₂₉ H ₂₆ ClF ₃ N ₄ O ₄ .2HCl
279812	CH2N(Et)CH2-CH2N(Et)2	H	2HCl	C ₃₂ H ₃₄ ClF ₃ N ₄ O ₄ .2HCl
279813	H	CH2N(Et)2	HCl	C ₂₈ H ₂₆ ClF ₃ N ₃ O ₄ .HCl
279814	H	4-morpholinyl-CH2	HCl	C ₂₈ H ₂₃ ClF ₃ N ₃ O ₅ .HCl
279815	H	4-Me-1-Piz-CH2	2HCl	C ₂₉ H ₂₆ ClF ₃ N ₄ O ₄ .2HCl
279816	H	CH2N(Et)CH2-CH2N(Et)2	2HCl	C ₃₂ H ₃₄ ClF ₃ N ₄ O ₄ .2HCl

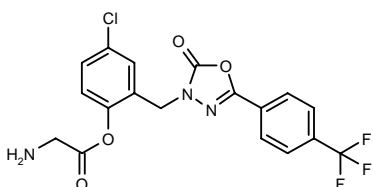
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Hewawasam, P. et al. (Bristol-Myers Squibb Co.) Benzoate derivs. of diaryl 1,3,4-oxadiazolone. US 5948802, WO 9938854.

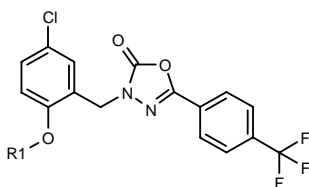
279817

Glycine 4-chloro-2-[2-oxo-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,3,4-oxadiazol-3-ylmethyl]phenyl ester



C18 H13 Cl F3 N3 O4; Mol wt: 427.7647

ACTION – Agent for the treatment of ischemia, stroke, convulsions, epilepsy, asthma, irritable bowel syndrome, migraine, traumatic brain injury, sexual dysfunction and urinary incontinence, a prodrug of a known large-conductance Ca^{2+} -activated potassium channel (BK_{Ca} channel) opener. Other compounds from this series of amino acid derivatives of diaryl 1,3,4-oxadiazolones include the following:



Compound	R1	Formula
279818	L-Ala	$\text{C}_{19}\text{H}_{15}\text{ClF}_3\text{N}_3\text{O}_4$
279819	$\text{COC}(\text{Me})_2\text{NH}_2$	$\text{C}_{20}\text{H}_{17}\text{ClF}_3\text{N}_3\text{O}_4$
279820	L-Leu	$\text{C}_{22}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_4$
279821	L-Lys	$\text{C}_{22}\text{H}_{22}\text{ClF}_3\text{N}_4\text{O}_4$
279822	L-Pro	$\text{C}_{21}\text{H}_{17}\text{ClF}_3\text{N}_3\text{O}_4$
279823	N-Me-Gly	$\text{C}_{19}\text{H}_{15}\text{ClF}_3\text{N}_3\text{O}_4$
279824	N-Me-L-Leu	$\text{C}_{23}\text{H}_{23}\text{ClF}_3\text{N}_3\text{O}_4$

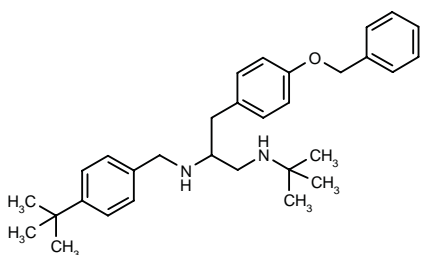
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Hewawasam, P. et al. (Bristol-Myers Squibb Co.) *Amino acid derivs. of diaryl 1,3,4-oxadiazolone*. US 5977150, WO 9938853.

279905

3-[4-(Benzyloxy)phenyl]- N^1 -(*tert*-butyl)- N^2 -[4-(*tert*-butyl)benzyl]-1,2-propanediamine



C31 H42 N2 O; Mol wt: 458.6858

ACTION – Calcium channel antagonist, an analogue of PD-151307 with an IC_{50} of 0.45 μM for blockade of calcium efflux through N-type calcium channels in human neuroblastoma IMR-32 cells and of 0.88 μM for blockade of smooth muscle L-type calcium channels in the A10 assay. Compound exhibited good efficacy in preventing tonic seizures in the audiogenic seizure model in DBA/2 mice (100% protection at 30 mg/kg i.v.). Potentially useful for the treatment of ischemic disorders, neurodegenerative disorders and epilepsy.

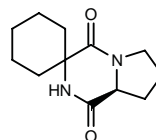
SOURCES – Elan; Parke-Davis (Warner-Lambert).

REFERENCES

1. Song, Y. et al. *Novel N-type calcium channel antagonists: SAR studies of PD 0151307 analogs*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MED1 264.

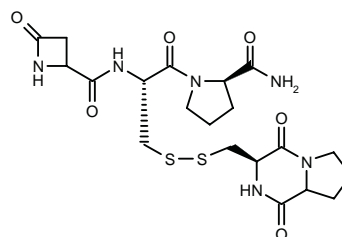
279948

(*S*)-Perhydrospiro[pyrrolo[1,2-*a*]pyrazine-3,1'-cyclohexane]-1,7-dione



C12 H18 N2 O2; Mol wt: 222.2862

ACTION – Neuroprotective agent for the treatment of CNS disorders, particularly injury resulting from brain or spinal cord trauma, stroke and neurodegenerative diseases such as Alzheimer's disease, as well as for enhancing memory, a thyrotropin-releasing hormone (TRH) analogue with an improved profile as compared to TRH by virtue of its resistance to enzymatic degradation by proteases, resulting in a longer half-life, and reduced analeptic and autonomic side effects. Neuroprotective and memory-enhancing effects were demonstrated in several *in vivo* models in mice and rats at a dose of 1 mg/kg i.v. Another compound from this series of bicyclic 2,5-diketopiperazines and 4-substituted-2-azetidinones is:



279949: C20 H28 N6 O6 S2

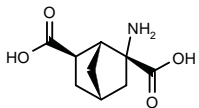
SOURCE – Georgetown University, Washington, DC (US).

REFERENCES

1. Kozikowski, A.P. et al. (Georgetown University) *Cyclic dipeptides and azetidinone cpds. and their use in treating CNS injury and neurodegenerative disorders*. WO 9940931.

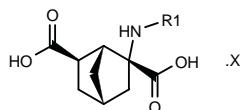
281220

(1*R**,2*R**,4*S**,6*R**)-2-Aminobicyclo[2.2.1]heptane-2,6-dicarboxylic acid



C₉H₁₃N O₄; Mol wt: 199.2047

ACTION – Selective class II metabotropic glutamate receptor ligand potentially useful for the treatment of a variety of neurological and psychiatric disorders such as stroke, cerebral ischemia, spinal cord and head trauma, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine, urinary incontinence, psychosis, convulsions, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug-induced Parkinson's disease, anxiety, schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, acute and chronic pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting. Other exemplified bicyclo[2.2.1]heptanes are:



Compound	R1	X	Formula
281221	H	HCl	C ₉ H ₁₃ NO ₄ ·HCl
281222	CH ₂ Ph		C ₁₆ H ₁₉ NO ₄
281223	CH ₂ CH ₂ Ph		C ₁₇ H ₂₁ NO ₄

SOURCE – Pfizer.

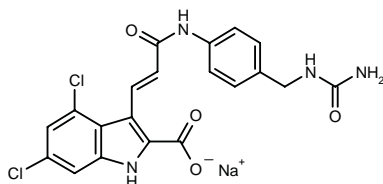
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1. Chenard, B.L. (Pfizer Products Inc.) *Bicyclo[2.2.1]heptanes and related cpds.* WO 9947490.

GV-228869*

241774

4,6-Dichloro-3-[2(*E*)-[*N*-[4-(ureidomethyl)phenyl]carbamoyl]vinyl]-1*H*-indole-2-carboxylic acid sodium salt



C₂₀H₁₅Cl₂N₄Na O₄; Mol wt: 469.2630

M.p. > 250 °C.

ACTION – Neuroprotective agent, a potent, noncompetitive antagonist of the NMDA receptor glycine binding site ($pK_i = 8.67$) with high selectivity for the strychnine-insensitive binding site over NMDA glutamate, AMPA and kainate binding sites ($pK_i = 3.48, 3.98$ and 4.68 , respectively and proven inactive against a panel of 70 different CNS receptors ($pK_i < 5$). Compound (0.1-3 mg/kg i.v.) showed significant, dose-dependent neuroprotective activity as both pre- and postischemia treatment in a model of rat focal cerebral ischemia; when administered preischemically (5 min prior to occlusion), it gave a maximal protection of 66% at 3 mg/kg i.v. ($ED_{50} = 0.2$ mg/kg) and was slightly more potent than the reference agents MK-801, GV-150526A and ACEA-1021. When given postischemically, compound provided significant neuroprotection even when treatment was delayed for up to 6 h. In mice, it protected against NMDA-induced convulsions ($ED_{50} = 0.07$ mg/kg i.v., 2 mg/kg p.o.) and was devoid of adverse effects such as ataxia at up to 30 mg/kg i.v.

SOURCE – Glaxo Wellcome.

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1. Conti, N. et al. (Glaxo Wellcome plc) *Indole derivs. as EAA antagonists.* EP 813524, JP 99501041, US 5919811, WO 9627588.

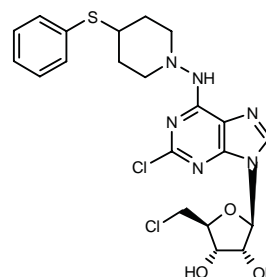
2. Di Fabio, R. et al. *Substituted analogues of GV150526 as potent glycine binding site antagonists in animal models of cerebral ischemia.* J Med Chem 1999, 42(18): 3486.

*Identified compound 241774 Drug Data Rep 1997, 019(01): 0030.

NNC-21-0147

279405

5'-Deoxy-2,5'-dichloro-*N*-[4-(phenylsulfanyl)-1-piperidin-yl]adenosine



C₂₁H₂₄Cl₂N₆O₃S; Mol wt: 511.4316

ACTION – Neuroprotective agent, an adenosine A₁ receptor agonist with a K_i of 3.6 nM for displacement of [³H]-*R*-PIA binding from rat brain A₁ receptors and approximately 300-fold selectivity over A₂ receptors ($K_i = 1150$ nM). In *in vitro* functional tests, compound showed full agonist activity, as demonstrated by inhibition of isoprenaline-induced cAMP accumulation in DDT-MF2 cells ($IC_{50} = 1.4$ nM). *In vivo*, it exhibited significant neuroprotective activity in two models of cerebral ischemia, achieving 45% protection against hippocampal cell death after 2 doses of 30 mg/kg i.p. in gerbils subjected to global ischemia, and approximately 50% protection after 2 doses of 0.05 mg/kg i.p. in mice with focal ischemia. In mice, compound was also shown to inhibit DMCM-induced seizures ($ED_{50} = 25$ mg/kg i.p.) and reduce body temperature (from 37 to 32 degrees

centigrade). Compound exhibited reduced effects on locomotor activity in mice (ED_{50} = 8.2 mg/kg i.p.) compared to reference A_2 agonists, as well as reduced cardiovascular effects, as demonstrated both *in vitro* by its small bradycardic effect in isolated guinea pig atria (EC_{50} = 25.5 μ M) and *in vivo* by only slight reduction in arterial blood pressure in anesthetized rats (10% at 0.1 mg/kg i.v.). Potentially useful for the treatment of cerebral ischemia

SOURCE – Novo Nordisk.

REFERENCES

1. Knutsen, L. et al. (Novo Nordisk A/S) *A method of treating disorders related to cytokines in mammals*. WO 9733591.

2. Lau, J. and Knutsen, L.J.S. (Novo Nordisk A/S) *Chemical cpds., their preparation and use*. EP 719275, JP 99511436, US 5589467, WO 9507921.

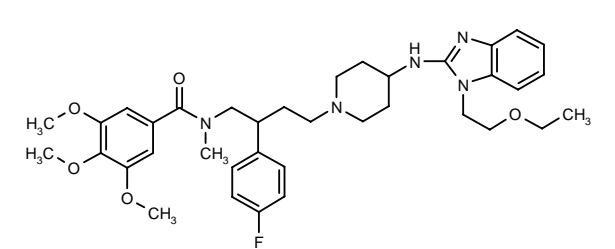
3. Knutsen, L.J.S. et al. *N-substituted adenosines as novel neuroprotective A_1 agonists with diminished hypotensive effects*. J Med Chem 1999, 42(18): 3463.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

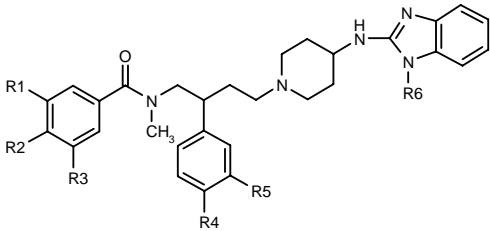
278791

N-[4-[4-[1-(2-Ethoxyethyl)-1*H*-benzimidazol-2-ylamino]piperidin-1-yl]-2-(4-fluorophenyl)butyl]-3,4,5-trimethoxy-*N*-methylbenzamide



C37 H48 F N5 O5; Mol wt: 661.8142

ACTION – Agent for the treatment of allergic rhinitis, asthma, emesis and inflammatory bowel disease with dual histamine and tachykinin receptor-antagonist activity. Other specifically claimed compounds from this series of substituted *N*-methyl-*N*-[4-[4-(1*H*-benzimidazol-2-yl-amino)piperidin-1-yl]-2-(aryl)butyl]benzamides include the following:



Compound	R1=R2=R3	R4	R5	R6	Formula
278793	H	Cl	Cl	CH2CH2OEt	C ₃₄ H ₄₁ Cl ₂ N ₅ O ₂
278794	OMe	F	H	CH2CH2OCH2CF3	C ₃₇ H ₄₅ F ₄ N ₅ O ₅
278796	OMe	F	H	4-F-PhCH2	C ₄₀ H ₄₅ F ₂ N ₅ O ₄
278797	OMe	F	H	3-furyl	C ₃₇ H ₄₂ FN ₅ O ₅
278798	OMe	F	H	2-furyl	C ₃₇ H ₄₂ FN ₅ O ₅

SOURCE – Hoechst Marion Roussel.

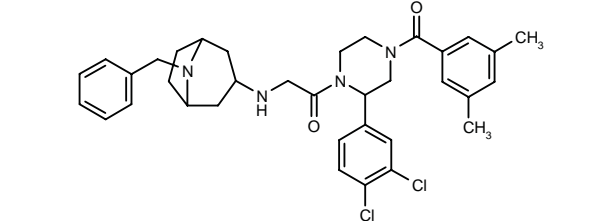
REFERENCES

1. Maynard, G.D. et al. (Hoechst Marion Roussel, Inc.) *Substd. N-methyl-N-(4-(4-(1*H*-benzimidazol-2-yl-amino)piperidin-1-yl)-2-(aryl)butyl)benzamides useful for the treatment of allergic diseases*. US 5922737.

ASTHMA THERAPY

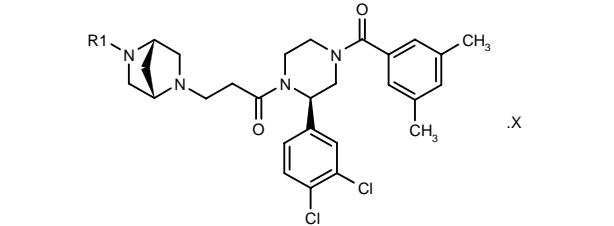
279216

2-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-ylamino)-1-[2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)piperazin-1-yl]-1-ethanone



C35 H40 Cl2 N4 O2; Mol wt: 619.6330

ACTION – Agent for the treatment of chronic airways disorders such as asthma and allergies, as well as inflammatory, CNS, gastrointestinal and autoimmune diseases and pain, that acts by virtue of its neurokinin receptor-antagonist activity. Other compounds from this series of substituted piperazine derivatives include the following:



Compound	R1	X	Formula
279217	H	2HCl	C ₂₇ H ₃₂ Cl ₂ N ₄ O ₂ ·2HCl
279218	3-thienyl-CH2		C ₃₂ H ₃₆ Cl ₂ N ₄ O ₂ S

centigrade). Compound exhibited reduced effects on locomotor activity in mice (ED_{50} = 8.2 mg/kg i.p.) compared to reference A_2 agonists, as well as reduced cardiovascular effects, as demonstrated both *in vitro* by its small bradycardic effect in isolated guinea pig atria (EC_{50} = 25.5 μ M) and *in vivo* by only slight reduction in arterial blood pressure in anesthetized rats (10% at 0.1 mg/kg i.v.). Potentially useful for the treatment of cerebral ischemia

SOURCE – Novo Nordisk.

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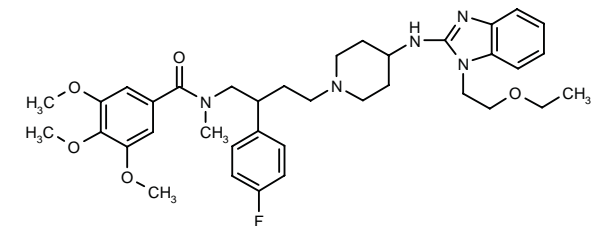
3. Knutsen, L.J.S. et al. *N-substituted adenosines as novel neuroprotective A_1 agonists with diminished hypotensive effects*. J Med Chem 1999, 42(18): 3463.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

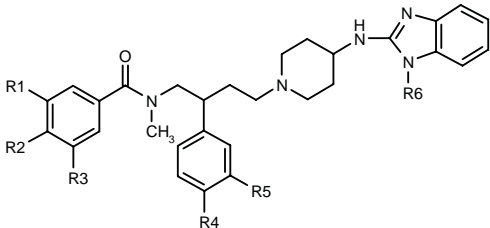
278791

N-[4-[4-[1-(2-Ethoxyethyl)-1*H*-benzimidazol-2-ylamino]piperidin-1-yl]-2-(4-fluorophenyl)butyl]-3,4,5-trimethoxy-*N*-methylbenzamide



C37 H48 F N5 O5; Mol wt: 661.8142

ACTION – Agent for the treatment of allergic rhinitis, asthma, emesis and inflammatory bowel disease with dual histamine and tachykinin receptor-antagonist activity. Other specifically claimed compounds from this series of substituted *N*-methyl-*N*-[4-[4-(1*H*-benzimidazol-2-yl-amino)piperidin-1-yl]-2-(aryl)butyl]benzamides include the following:



Compound	R1=R2=R3	R4	R5	R6	Formula
278793	H	Cl	Cl	CH2CH2OEt	C ₃₄ H ₄₁ Cl ₂ N ₅ O ₂
278794	OMe	F	H	CH2CH2OCH2CF3	C ₃₇ H ₄₅ F ₄ N ₅ O ₅
278796	OMe	F	H	4-F-PhCH2	C ₄₀ H ₄₅ F ₂ N ₅ O ₄
278797	OMe	F	H	3-furyl	C ₃₇ H ₄₂ FN ₅ O ₅
278798	OMe	F	H	2-furyl	C ₃₇ H ₄₂ FN ₅ O ₅

SOURCE – Hoechst Marion Roussel.

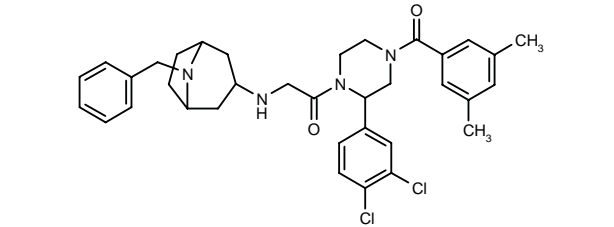
REFERENCES

1. Maynard, G.D. et al. (Hoechst Marion Roussel, Inc.) *Substd. N-methyl-N-(4-(4-(1*H*-benzimidazol-2-yl-amino)piperidin-1-yl)-2-(aryl)butyl)benzamides useful for the treatment of allergic diseases*. US 5922737.

ASTHMA THERAPY

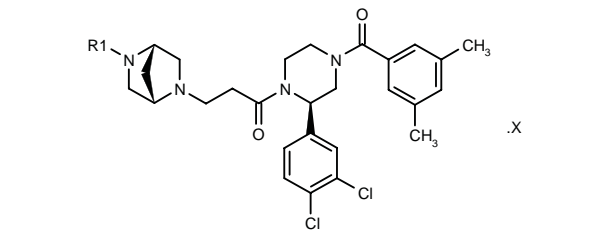
279216

2-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-ylamino)-1-[2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)piperazin-1-yl]-1-ethanone

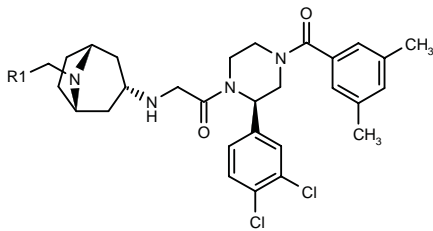


C35 H40 Cl2 N4 O2; Mol wt: 619.6330

ACTION – Agent for the treatment of chronic airways disorders such as asthma and allergies, as well as inflammatory, CNS, gastrointestinal and autoimmune diseases and pain, that acts by virtue of its neurokinin receptor-antagonist activity. Other compounds from this series of substituted piperazine derivatives include the following:



Compound	R1	X	Formula
279217	H	2HCl	C ₂₇ H ₃₂ Cl ₂ N ₄ O ₂ ·2HCl
279218	3-thienyl-CH2		C ₃₂ H ₃₆ Cl ₂ N ₄ O ₂ S



Compound	R1	Formula
279219	2-thienyl	C ₃₃ H ₃₈ Cl ₂ N ₄ O ₂ S
279220	4-(AcNH)-Ph	C ₃₇ H ₄₃ Cl ₂ N ₅ O ₃

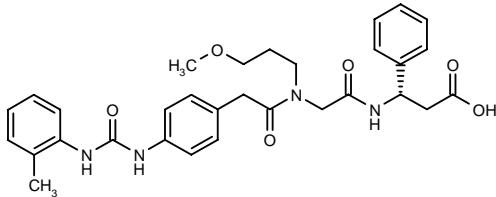
SOURCE – Schering-Plough.

REFERENCES

1. Shue, H.-J. et al. (Schering Corp.) *Piperazine derivs. as neurokinin antagonists*. WO 9936424.

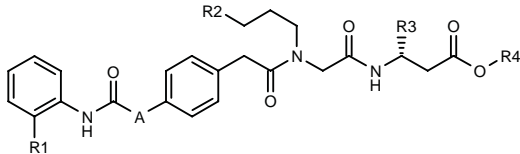
279358

3(S)-[2-[N-(3-Methoxypropyl)-2-[4-[3-(2-methylphenyl)-ureido]phenyl]acetamido]acetamido]-3-phenylpropionic acid



C31 H36 N4 O6; Mol wt: 560.6474

ACTION – Agent for the treatment of inflammatory, immune or autoimmune diseases, particularly inflammatory airways diseases, as well as for the prevention of transplant rejection, a cell adhesion inhibitor with nanomolar affinity for VLA-4 (also known as $\alpha_4\beta_1$ integrin or CD49d/CD29) receptors and very good antagonist activity. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
279359	Me	OMe	CH=CHMe	H	NH	C ₂₈ H ₃₆ N ₄ O ₆
279360	Me	OMe	3,4-(MeO)2-Ph	H	NH	C ₃₃ H ₄₀ N ₄ O ₈
279361	Me	OMe	4-MeO-Ph	Na	NH	C ₃₂ H ₃₇ N ₄ NaO ₇
279362	Me	CH2OMe	3,4-(MeO)2-Ph	H	NH	C ₃₄ H ₄₂ N ₄ O ₈
279363	Me	CH2OMe	Ph	H	NH	C ₃₂ H ₃₈ N ₄ O ₆
279364	Me	OMe	4-MeO-Ph	H	CH2	C ₃₃ H ₃₉ N ₃ O ₇
279365	H	OMe	Ph	H	NH	C ₃₀ H ₃₄ N ₄ O ₆
279366	Cl	OMe	Ph	H	NH	C ₃₀ H ₃₃ ClN ₄ O ₆
279367	NH2	OMe	Ph	H	NH	C ₃₀ H ₃₅ N ₅ O ₆

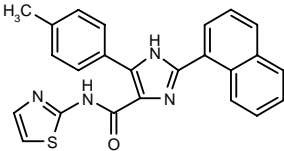
SOURCE – Novartis.

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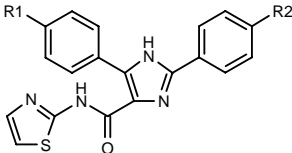
279395

5-(4-Methylphenyl)-2-(1-naphthyl)-N-(2-thiazolyl)-1 H-imidazole-4-carboxamide



C24 H18 N4 O S; Mol wt: 410.4992

ACTION – Agent for the treatment of allergic disorders such as atopic dermatitis, bronchial asthma and allergic rhinitis, a potent inhibitor of the production of IL-4 and IL-5 (IC₅₀ = 0.91 and 0.33 μ M, respectively, in Th2 cells). *In vivo*, it was found to inhibit ovalbumin-induced ear edema at 10 mg/kg p.o. in sensitized mice. Other compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	Formula
279396	OMe	NO2	C ₂₀ H ₁₅ N ₅ O ₄ S
279397	OMe	N(Me)2	C ₂₂ H ₂₁ N ₅ O ₂ S
279398	NHMe	t-Bu	C ₂₄ H ₂₅ N ₅ OS

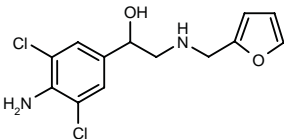
SOURCE – Yoshitomi.

REFERENCES

1. Sueoka, H. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Novel imidazole derivs*. WO 9933827.

279673

1-(4-Amino-3,5-dichlorophenyl)-2-(2-furylmethylamino)-ethan-1-ol



C13 H14 Cl2 N2 O2; Mol wt: 301.1716

ACTION – Bronchodilating agent, a phenylethanolamine derivative proven to be more active than clorprenaline in relaxing bronchi contracted by acetylcholine *in vitro*.

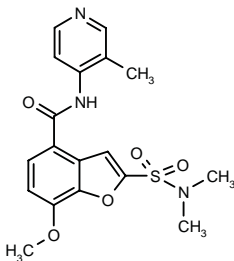
SOURCE – Shenyang Pharmaceutical University, Shenyang (CN).

REFERENCES

1. Huo, C.H. et al. *Synthesis and bronchodilating activity of phenylethanolamine derivatives*. Chin J Med Chem 1999, 9(2): 94.

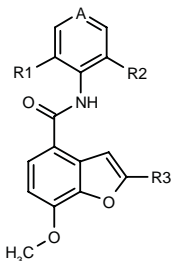
279760

2-(*N,N*-Dimethylsulfamoyl)-7-methoxy-*N*-(3-methylpyridin-4-yl)benzofuran-4-carboxamide



C18 H19 N3 O5 S; Mol wt: 389.4301

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4) and of the production of TNF, with potential in the treatment of a broad range of disorders including asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, CNS disorders such as depression and multiinfarct dementia, AIDS and septic shock. Other specifically claimed compounds from this series of benzofuran-4-carboxamides include the following:



Compound	R1	R2	R3	A	Formula
279761	Cl	Cl	cyclopropyl-CH2OCH2	NO	C ₂₀ H ₁₈ Cl ₂ N ₂ O ₅
279762	Cl	Cl	1-Me-4-Pip-OCH2	NO	C ₂₂ H ₂₃ Cl ₂ N ₃ O ₅
279763	H	Me	SO2Me	N	C ₁₇ H ₁₆ N ₂ O ₅ S
279765	Me	H	SO2N(Me)2	NO	C ₁₈ H ₁₉ N ₃ O ₅ S
279766	Me	H	cyclopropyl-CH(OH)	NO	C ₂₀ H ₂₀ N ₂ O ₅
279808	Me	H	SO2Me	NO	C ₁₇ H ₁₆ N ₂ O ₅ S

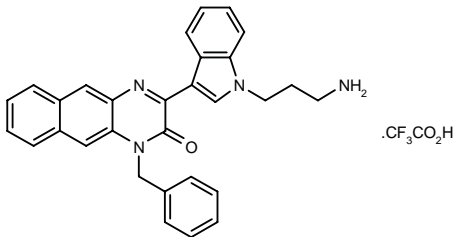
SOURCE – Darwin Discovery.

REFERENCES

1. Dyke, H.J. et al. (Darwin Discovery Ltd.) *Benzofuran-4-carboxamides and their therapeutic use*. WO 9940085.

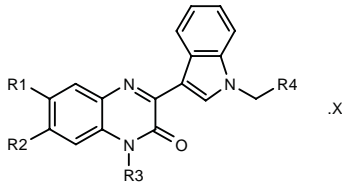
281224

3-[1-(3-Aminopropyl)-1*H*-indol-3-yl]-1-benzylbenzo[*g*]-quinoxalin-2(1*H*)-one trifluoroacetate



C30 H26 N4 O . C2 H F3 O2; Mol wt: 572.5843

ACTION – Protein kinase C (PKC) inhibitor potentially useful in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or neurodegenerative disorders. More specifically, it is indicated for oral or topical use in the treatment of asthma, bronchitis, atopic diseases such as rhinitis and atopic dermatitis, inflammatory bowel disease, autoimmune diseases such as multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus and rheumatoid arthritis, malignant diseases, HIV infection or AIDS and for inhibiting transplant rejection. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	X	Formula
281225	-CH=CHCH=CH-	CH2-CO2Me	H	CH2CH2-NH2	CF3CO2H	C ₂₆ H ₂₄ N ₄ O ₃ .C ₂ HF ₃ O ₂
281226	-(CH2)3-	H	H	3-(NH2-CH2)-Ph	acetate	C ₂₇ H ₂₄ N ₄ O .C ₂ H ₄ O ₂
281228	-(CH2)4-	H	H	6-(NH2-CH2)-2-Pyr	acetate	C ₂₇ H ₂₅ N ₅ O .C ₂ H ₄ O ₂

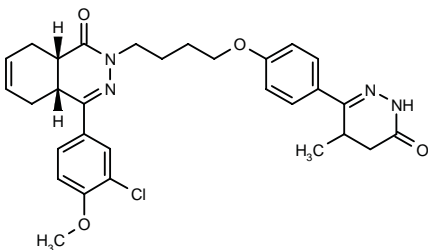
SOURCE – AstraZeneca.

REFERENCES

1. Karabelas, K. and Sjö, P. (Astra AB) *New cpds*. WO 9946264.

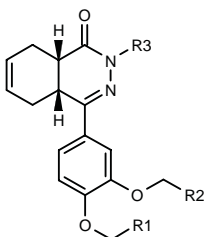
281282

cis-4-(3-Chloro-4-methoxyphenyl)-2-[4-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy]butyl]-1,2,4a,5,8,8a-hexahydrophthalazin-1-one



C30 H33 Cl N4 O4; Mol wt: 549.0677

ACTION – Phosphodiesterase type 3 (PDE3) and 4 (PDE4) inhibitor ($-\log IC_{50} = 7.45$ and 7.77 , respectively), with potential in the treatment of airways disorders. Other compounds from this series of phthalazinone derivatives include the following:



Compound	R1=R2	R3	Formula
281283	H	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-Ph	C ₂₇ H ₂₈ N ₄ O ₄
281284	H	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-PhNHCOCH ₂	C ₂₉ H ₃₁ N ₅ O ₅
281285	H	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-PhNHCO(CH ₂) ₂ C(Me)	C ₃₂ H ₃₇ N ₅ O ₅
281286	H	4-[4-(6-oxo-1,6-dihydro-3-pyridazinyl)-PhNHCO]-Ph	C ₃₃ H ₂₉ N ₅ O ₅
281287	Me	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-Ph	C ₂₉ H ₃₂ N ₄ O ₄
281288	Me	4-(4-Me-6-oxo-1,4,5,6-tetrahydro-3-pyridazinyl)-PhO(CH ₂) ₄	C ₃₃ H ₄₀ N ₄ O ₅

SOURCE – Byk Gulden.

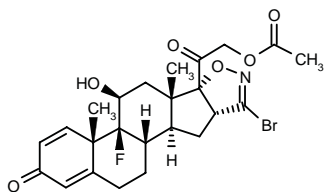
REFERENCES

1. Katzelmann, A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phthalazinone PDE III/IV inhibitors*. WO 9947505.

GT-261163X

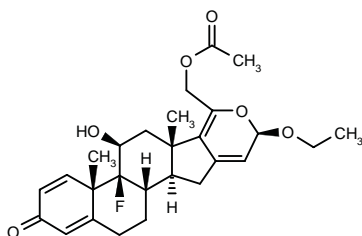
279486

21-Acetoxy-3'-bromo-9β-fluoro-11β-hydroxyisoxazolo-[4',5':16,17]pregna-1,4-diene-3,20-dione



C₂₄ H₂₇ Br F N O₆; Mol wt: 524.3803

ACTION – Steroid with good glucocorticoid activity and good plasma stability, potentially useful for the treatment of asthma. Within this class of steroidal 17α-hydroxy,16α-acetic acid-γ-lactones, the following is also included:



GT-250632X [279488]: C₂₇ H₃₃ F O₆

SOURCE – Affymax.

REFERENCES

1. Ramesh, U.V. et al. *Synthesis and activity of steroidal 17α-hydroxy, 16α-acetic acid-γ-lactones*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 83.

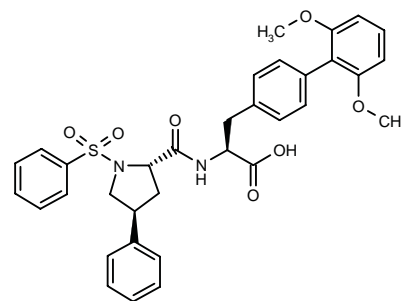
TR-14531

279572

3-(2',6'-Dimethoxybiphenyl-4-yl)-2(S)-[4(S)-phenyl-1-(phenylsulfonyl)pyrrolidin-2(S)-ylcarboxamido]propionic acid

N-(Phenylsulfonyl)-4(S)-phenyl-L-prolyl-3-(2',6'-dimethoxybiphenyl-4-yl)-L-alanine

N-(Phenylsulfonyl)-4(S)-phenyl-L-prolyl-4-(2,6-dimethoxyphenyl)-L-phenylalanine



C₃₄ H₃₄ N₂ O₇ S; Mol wt: 614.7156

ACTION – Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration including asthma, rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis. Compound strongly antagonized $\alpha_4\beta_1$ integrin-mediated cell adhesion with an IC_{50} of 1 nM and 600-fold selectivity relative to $\alpha_4\beta_7$ integrin.

SOURCE – Tanabe Seiyaku.

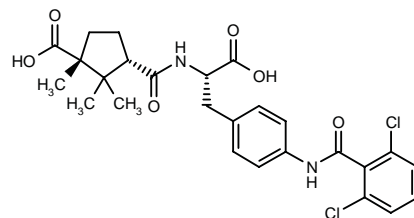
REFERENCES

1. Furth, P.S. et al. *Parallel-synthesis optimization of TR-14035, a dual-active $\alpha_4\beta_7/\alpha_4\beta_1$ integrin antagonist: Generation of $\alpha_4\beta_7$ selective antagonists*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 61.

TR-9109*

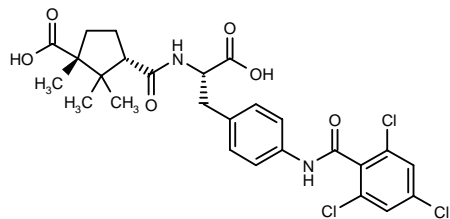
272076

N-[3(*R*)-Carboxy-2,2,3-trimethylcyclopent-1(*S*)-ylcarbon-yl]-4-(2,6-dichlorobenzamido)-L-phenylalanine



C₂₆ H₂₈ Cl₂ N₂ O₆; Mol wt: 535.4212

ACTION – Small-molecule cell adhesion inhibitor that acts as an antagonist of VLA-4 (very late antigen-4, CD49/CD29 or $\alpha_4\beta_1$) integrin and thereby blocks the binding of VLA-4 to VCAM-1 and fibronectin (IC_{50} = 21 and 5 nM, respectively). Potentially useful in the treatment or prevention of inflammatory and allergic disorders. Another related compound is:



279906: C26 H27 Cl3 N2 O6

SOURCES – Pharmacia & Upjohn; Tanabe Seiyaku.

REFERENCES

1. Lobl, T.J. et al. (Tanabe Seiyaku Co., Ltd.; Pharmacia & Upjohn Co.) *Inhibitors of $\alpha_4\beta_1$ mediated cell adhesion*. WO 9858902.

2. Teegarden, B.R. et al. *Discovery of TR-9109: A novel small molecule inhibitor of $\alpha_4\beta_1$ integrin mediated cell adhesion*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 58.

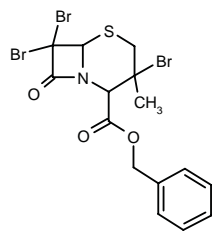
*Identified compound **272076** (see **272074**) Drug Data Rep 1999, 021(03): 0257.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME AND EMPHYSEMA

280150

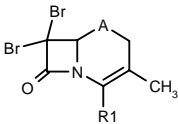
3,7,7-Tribromo-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-octane-2-carboxylic acid benzyl ester

3,7,7-Tribromo-3-methylcepham-4-carboxylic acid benzyl ester

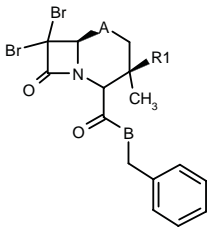


C15 H14 Br3 N O3 S; Mol wt: 528.0576

ACTION – An inhibitor of proteases, particularly human leukocyte elastase, with potential in the treatment and prevention of diseases caused by the uncontrolled release of proteolytic enzymes, particularly emphysema, metastasis and cystic fibrosis. Other exemplified compounds within this series of 7-bromo- and 7,7-dibromo-cepham and cephem derivatives include the following:



Compound	R1	A	Formula
280151	H	S	C ₇ H ₇ Br ₂ NOS
280152	H	SO	C ₇ H ₇ Br ₂ NO ₂ S
280153	CO ₂ CH ₂ Ph	S	C ₁₅ H ₁₃ Br ₂ NO ₃ S
280156	CONHCH ₂ Ph	S	C ₁₅ H ₁₄ Br ₂ N ₂ O ₂ S



Compound	R1	A	B	Formula
280154	OH	S	O	C ₁₅ H ₁₅ Br ₂ NO ₄ S
280155	Br	S	NH	C ₁₅ H ₁₅ Br ₃ N ₂ O ₂ S
280157	Br	SO ₂	NH	C ₁₅ H ₁₅ Br ₃ N ₂ O ₄ S

SOURCE – Pliva.

REFERENCES

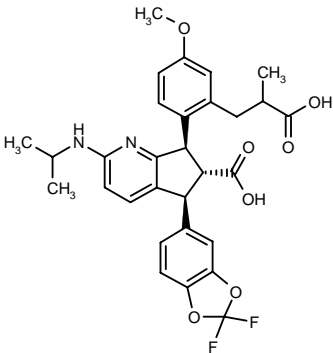
1. Lukic, I. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *7-Bromo- and 7,7-dibromo-cepham and cephem derivs. and their use as protease inhibitors*. CA 2256002, EP 934944, JP 99255771.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

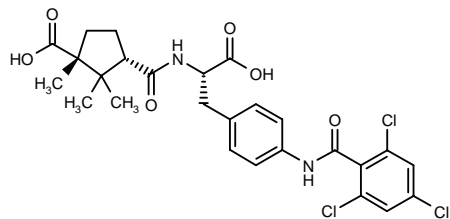
279589

7(*R*)-[2-(2-Carboxypropyl)-4-methoxyphenyl]-5(*S*)-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(isopropylamino)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6(*R*)-carboxylic acid



C30 H30 F2 N2 O7; Mol wt: 568.5700

ACTION – Small-molecule cell adhesion inhibitor that acts as an antagonist of VLA-4 (very late antigen-4, CD49/CD29 or $\alpha_4\beta_1$) integrin and thereby blocks the binding of VLA-4 to VCAM-1 and fibronectin (IC_{50} = 21 and 5 nM, respectively). Potentially useful in the treatment or prevention of inflammatory and allergic disorders. Another related compound is:



279906: C26 H27 Cl3 N2 O6

SOURCES – Pharmacia & Upjohn; Tanabe Seiyaku.

REFERENCES

1. Lobl, T.J. et al. (Tanabe Seiyaku Co., Ltd.; Pharmacia & Upjohn Co.) *Inhibitors of $\alpha_4\beta_1$ mediated cell adhesion*. WO 9858902.

2. Teegarden, B.R. et al. *Discovery of TR-9109: A novel small molecule inhibitor of $\alpha_4\beta_1$ integrin mediated cell adhesion*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 58.

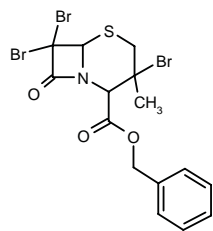
*Identified compound **272076** (see **272074**) Drug Data Rep 1999, 021(03): 0257.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME AND EMPHYSEMA

280150

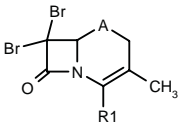
3,7,7-Tribromo-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-octane-2-carboxylic acid benzyl ester

3,7,7-Tribromo-3-methylcepham-4-carboxylic acid benzyl ester

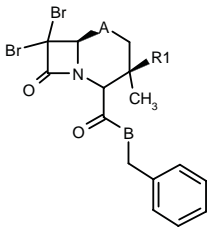


C15 H14 Br3 N O3 S; Mol wt: 528.0576

ACTION – An inhibitor of proteases, particularly human leukocyte elastase, with potential in the treatment and prevention of diseases caused by the uncontrolled release of proteolytic enzymes, particularly emphysema, metastasis and cystic fibrosis. Other exemplified compounds within this series of 7-bromo- and 7,7-dibromo-cepham and cephem derivatives include the following:



Compound	R1	A	Formula
280151	H	S	C ₇ H ₇ Br ₂ NOS
280152	H	SO	C ₇ H ₇ Br ₂ NO ₂ S
280153	CO ₂ CH ₂ Ph	S	C ₁₅ H ₁₃ Br ₂ NO ₃ S
280156	CONHCH ₂ Ph	S	C ₁₅ H ₁₄ Br ₂ N ₂ O ₂ S



Compound	R1	A	B	Formula
280154	OH	S	O	C ₁₅ H ₁₅ Br ₂ NO ₄ S
280155	Br	S	NH	C ₁₅ H ₁₅ Br ₃ N ₂ O ₂ S
280157	Br	SO ₂	NH	C ₁₅ H ₁₅ Br ₃ N ₂ O ₄ S

SOURCE – Pliva.

REFERENCES

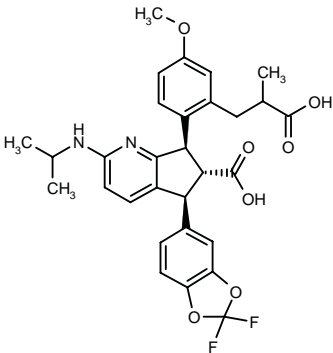
1. Lukic, I. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) *7-Bromo- and 7,7-dibromo-cepham and cephem derivs. and their use as protease inhibitors*. CA 2256002, EP 934944, JP 99255771.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

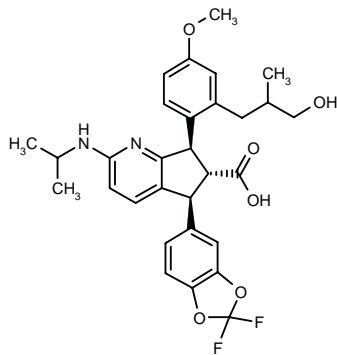
279589

7(*R*)-[2-(2-Carboxypropyl)-4-methoxyphenyl]-5(*S*)-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(isopropylamino)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6(*R*)-carboxylic acid



C30 H30 F2 N2 O7; Mol wt: 568.5700

ACTION – Potent and selective endothelin ET_A receptor antagonist with IC₅₀ values of 0.056 and 78 nM, respectively, for human ET_A and ET_B receptors in a binding assay. Potentially useful in the treatment of hypertension, pulmonary hypertension, Raynaud’s disease, acute renal failure, heart failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatism, endotoxic shock, endotoxin-induced multiple organ failure and disseminated intravascular coagulation, and ciclosporin-induced renal failure and hypertension. Another representative substituted 5-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopentenopyridine derivatives is:



279590: C30 H32 F2 N2 O6

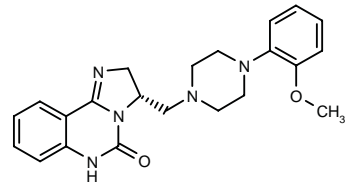
SOURCE – Banyu.

REFERENCES

1. Hayama, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Substd. 5-(2,2-difluoro-1,3-benzodioxol-5-yl) cyclopentenopyridine deriv.* WO 9937639.

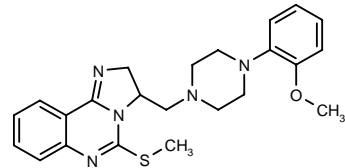
280208

(–)-3(*S*)-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazolin-5-one

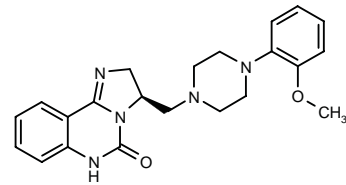


C22 H25 N5 O2; Mol wt: 391.4725

ACTION – Agent for the treatment of hypertension and dysuria with potent affinity for α₁-adrenoceptors (K_i = 0.1 nM against [³H]-prazosin binding in rat brain cortex homogenates). Other compounds from this series of optically active 2,3-dihydroimidazo[1,2-*c*]quinazoline derivatives include the following:



Compound	Isomer	Formula
280209	(+)-S	C ₂₃ H ₂₇ N ₅ OS
280210	(-)-R	C ₂₃ H ₂₇ N ₅ OS



280211: C22 H25 N5 O2

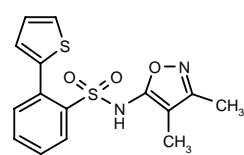
SOURCE – National Science Council, Taiwan, Taipei (TW).

REFERENCES

1. Chern, J.-W. et al. (National Science Council, Taiwan) *Optically active 2,3-dihydroimidazo(1,2-*c*)quinazoline derivs., the preparation and antihypertensive use thereof.* US 5932584.

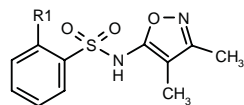
280224

N-(3,4-Dimethylisoxazol-5-yl)-2-(2-thienyl)benzenesulfonamide



C15 H14 N2 O3 S2; Mol wt: 334.4186

ACTION – Antihypertensive agent with endothelin receptor-antagonist activity. Other specifically claimed compounds from this series of heteroaryl-substituted phenyl isoxazole sulfonamides include the following:



Compound	R1	Formula
280225	3-thienyl	C ₁₅ H ₁₄ N ₂ O ₃ S ₂
280226	2-Pyr	C ₁₆ H ₁₅ N ₃ O ₃ S
280227	1-(PhSO2)-3-indolyl	C ₂₅ H ₂₁ N ₃ O ₅ S ₂
280228	3-indolyl	C ₁₉ H ₁₇ N ₃ O ₃ S
280229	1-(PhSO2)-2-indolyl	C ₂₅ H ₂₁ N ₃ O ₅ S ₂
280230	2-pyrimidinyl	C ₁₅ H ₁₄ N ₄ O ₃ S
280231	3-Pyr	C ₁₆ H ₁₅ N ₃ O ₃ S
280232	2-indolyl	C ₁₉ H ₁₇ N ₃ O ₃ S

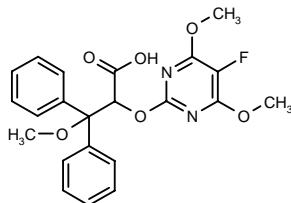
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Murugesan, N. and Barrish, J.C. (Bristol-Myers Squibb Co.) *Heteroaryl substd. phenyl isoxazole sulfonamide endothelin antagonists.* US 5939446.

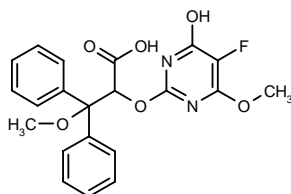
280273

3,3-Diphenyl-2-(5-fluoro-4,6-dimethoxypyrimidin-2-yloxy)-3-methoxypropionic acid



C22 H21 F N2 O6; Mol wt: 428.4139

ACTION – Endothelin antagonist with selectivity for ET_A receptors ($K_i = 7.4$ and 1200 nM, respectively, for ET_A and ET_B receptors), expected to have potential in the treatment of disorders such as hypertension, pulmonary hypertension, chronic heart failure, restenosis, acute and chronic renal failure, cerebral ischemia, asthma and benign prostatic hyperplasia. Another representative compound from this series of 5-substituted pyrimidin-2-yloxy carboxylic acid derivatives is:



280274: C21 H19 F N2 O6

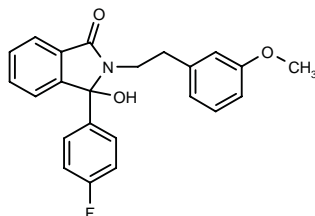
SOURCE – BASF.

REFERENCES

1. Amberg, W. et al. (BASF AG) *5-Subst. pyrimidine-2-yloxy carboxylic acid derivs., the production of the same and their utilization as endothelin antagonists*. DE 19806438, WO 9942453.

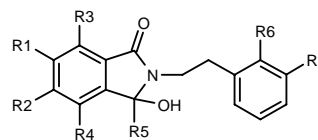
280279

3-(4-Fluorophenyl)-3-hydroxy-2-[2-(3-methoxyphenyl)-ethyl]-1-isoindolinone



C23 H20 F N O3; Mol wt: 377.4130

ACTION – Agent for the treatment of disorders involving low cGMP levels such as hypertension, angina pectoris, congestive heart failure, thrombosis, atherosclerosis, restenosis, stroke, erectile dysfunction, bronchial asthma, renal failure, diabetes and liver cirrhosis. *In vitro*, compound was shown to produce a 16-fold increase in cGMP levels at 50 μ M in an enzyme immunoassay using soluble guanylate cyclase. Other compounds from this series of substituted isoindolones include the following:



Compound	R1=R2=R3=R4	R5	R6	R7	Formula
280281	H	Ph	H	OMe	C ₂₃ H ₂₁ NO ₃
280283	H	cyclopentyl	Cl	H	C ₂₁ H ₂₂ ClNO ₂
280284	H	4-Pyr	H	OMe	C ₂₂ H ₂₀ N ₂ O ₃
280285	F	4-F-Ph	H	OMe	C ₂₃ H ₁₆ F ₅ NO ₃

SOURCE – Hoechst Marion Roussel.

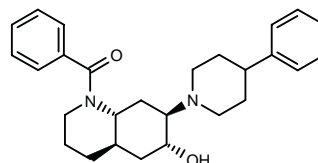
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ANTIARRHYTHMIC DRUGS

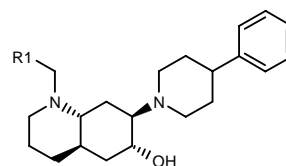
279272

1-[(4a,8a-*trans*:6,7-*trans*)-6-Hydroxy-7-(4-phenylpiperidin-1-yl)]perhydroquinolin-1-yl]-1-phenylmethanone



C27 H34 N2 O2; Mol wt: 418.5776

ACTION – Anticholinergic agent, an inhibitor of the vesicular acetylcholine transporter (VACHT) with an improved profile as compared to the known VACHT inhibitor vesamicol by virtue of its increased selectivity for VACHT and reduced lipophilicity, which leads to enhanced CNS penetration. *In vitro*, compound exhibited enhanced affinity for VACHT as compared to vesamicol ($K_i = 0.30 \pm 0.06$ nM vs. 2.0 ± 1.0 nM for (–)-vesamicol), while showing reduced affinity for σ_1 - and σ_2 -receptors ($K_i = 110.1 \pm 17.3$ and 233 ± 145 nM, respectively, vs. 26 ± 8 and 34 ± 2 nM, respectively, for (–)-vesamicol). Claimed for the treatment of cardiac arrhythmias. Other compounds from this series of decahydroquinoline derivatives include the following:



Compound	R1	Isomer	Formula
279273	CH=CHI	racemic	C ₂₃ H ₃₃ N ₂ O
279274	3-I-Ph	racemic	C ₂₇ H ₃₅ N ₂ O
279275	3-I-Ph	A	C ₂₇ H ₃₅ N ₂ O

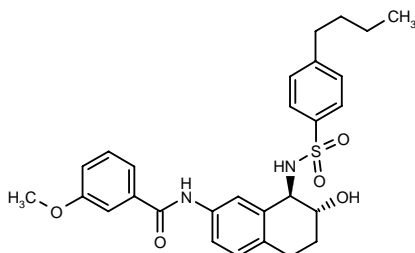
SOURCE – University of Minnesota, Minneapolis, MN (US).

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1. Efange, S.M.N. and Parsons, S.M. (University of Minnesota) *Decahydroquinoline-based anti-cholinergic agents*. US 5929087.

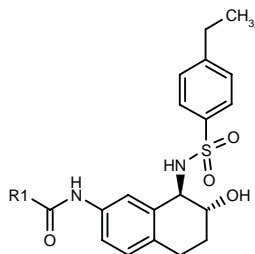
279294

trans-N-[8-(4-Butylphenylsulfonamido)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl]-3-methoxybenzamide



C28 H32 N2 O5 S; Mol wt: 508.6358

ACTION – Agent for the treatment of cardiac arrhythmias, as well as proliferative disorders, disorders of the auditory system, CNS-mediated motor dysfunction and disorders of pulmonary, vascular and visceral smooth muscle contractility, a potassium channel blocker with an IC_{50} value of 0.05 μ M when tested *in vitro* in electrophysiological studies for its inhibitory effect on ionic currents through the Kv1.5 channel in CHO cells; it also inhibited $^{86}Rb^+$ efflux through Kv1.5 channels expressed in CHO cells with an IC_{50} of 2.9 μ M. A representative compound within a series of bicyclic derivatives, wherein the following are also included:



Compound	R1	Formula
279295	3-MeO-Ph	C ₂₆ H ₂₈ N ₂ O ₅ S
279296	2-Et-1,2,3,4-tetrahydro-3-isoquinolinyl	C ₃₀ H ₃₅ N ₃ O ₄ S
279297	Ph-ethynylene	C ₂₇ H ₂₆ N ₂ O ₄ S

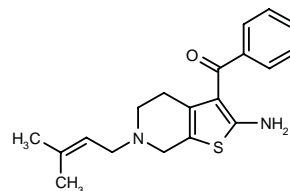
SOURCE – ICAGEN.

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1. Gross, M.F. and Castle, N.A. (ICAGEN, Inc.) *Potassium channel inhibitors*. WO 9937607.

280222

1-[2-Amino-6-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-1-phenylmethanone



C19 H22 N2 O S; Mol wt: 326.4618

ACTION – Agent for the treatment of adenosine-sensitive cardiac arrhythmias, pain, convulsions and for protection against hypoxia- and ischemia-induced injury that acts as an allosteric modulator of adenosine A₁ receptors, as demonstrated in binding and functional assays. A representative compound from a series of thiophene derivatives.

SOURCE – Medco.

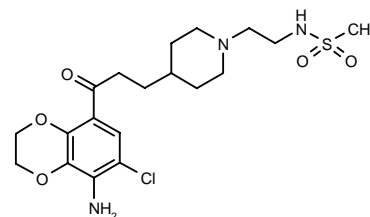
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RS-100302

279592

N-[2-[4-[3-(8-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-3-oxopropyl]piperidin-1-yl]ethyl]methanesulfonamide



C19 H28 Cl N3 O5 S; Mol wt: 445.9652

ACTION – Antiarrhythmic agent, a potent 5-HT₄ receptor antagonist, as demonstrated against 5-HT₄ receptor-mediated relaxation of carbachol-contracted rat esophageal muscularis mucosae ($pK_b = 9.9$). In pigs, compound produced significant atrial electrophysiological and antiarrhythmic effects against pacing-induced atrial fibrillation and atrial flutter, without producing ventricular proarrhythmic effects.

SOURCE – Roche Bioscience.

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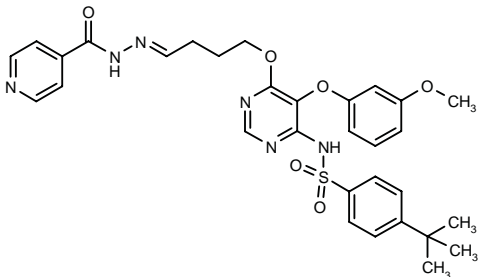
1. Clark, R.D. et al. (Syntex [USA], Inc.) *Novel 1-phenylalkane 5-HT₄ receptor ligands*. EP 700383, JP 96510743, WO 9427965.
2. Clark, R.D. et al. *RS-100235: A high affinity 5-HT₄ receptor antagonist*. Bioorg Med Chem Lett 1995, 5(18): 2119.

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4. Rahme, M.M. et al. *Electrophysiological and antiarrhythmic effects of the atrial selective 5-HT₄ receptor antagonist RS-100302 in experimental atrial flutter and fibrillation*. Circulation 1999, 100(19): 2010.

HEART FAILURE THERAPY

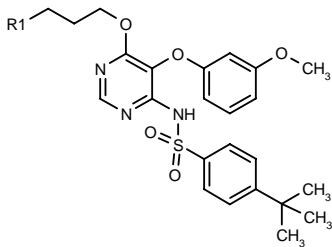
279422

*N*²-[4-[6-(4-*tert*-Butylphenylsulfonamido)-5-(3-methoxyphenoxy)pyrimidin-4-yloxi]butylidene]pyridine-4-carbohydrazide



C31 H34 N6 O6 S; Mol wt: 618.7116

ACTION – Agent for the treatment of cardiovascular disorders, a potent endothelin receptor antagonist with selective affinity for ET_B over ET_A receptors (IC₅₀ = 0.15 nM for displacement of [¹²⁵I]-ET-3 binding to ET_B receptors expressed in COS-7 cells vs. IC₅₀ = 340 nM for displacement of [¹²⁵I]-ET-1 binding to ET_A receptors in rat aortic smooth muscle; ET_A/ET_B ratio = 2267). Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	Formula
279423	CH=C(Ac)COBu	C ₃₃ H ₄₁ N ₃ O ₇ S
279424	CH=NNHCOPh	C ₃₂ H ₃₅ N ₅ O ₆ S
279425	3-Pyr-CONHN=CH	C ₃₁ H ₃₄ N ₆ O ₆ S
279426	4-OH-PhCONHN=CH	C ₃₂ H ₃₅ N ₅ O ₇ S
279427	2-thienyl-CONHN=CH	C ₃₀ H ₃₃ N ₅ O ₆ S ₂
279428	2-furyl-CONHN=CH	C ₃₀ H ₃₃ N ₅ O ₇ S
279429	CH=NNHCOCONH2	C ₂₇ H ₃₂ N ₆ O ₇ S
279430	CH=NNHSO2Ph	C ₃₁ H ₃₅ N ₅ O ₇ S ₂

SOURCE – Shionogi.

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1. Kawanishi, Y. and Araki, Y. (Shionogi & Co. Ltd.) *Novel pyrimidine derivs*. WO 9936408.

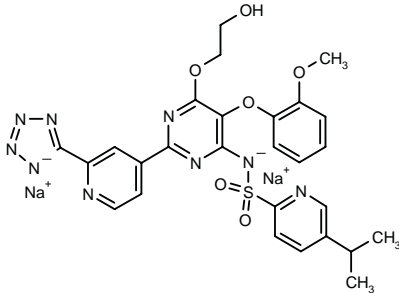
TEZOSENTAN DISODIUM*
Prop INN

279345

239527 (as free acid)

N-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide disodium salt

Ro-61-0612



C27 H25 N9 Na2 O6 S; Mol wt: 649.5975

ACTION – Potent endothelin receptor antagonist with nanomolar affinity for both ET_A and ET_B receptors (K_i = 0.3 and 18 nM, respectively, for ET_A receptors expressed in CHO cells and in baculovirus-infected Sf9 insect cells; K_i = 21 and 11 nM, respectively, for ET_B receptors from human placenta and porcine trachea). In *in vitro* functional tests, compound exhibited full antagonist activity, with a pA₂ of 9.5 for inhibition of ET-1-induced contractions in rat aortic rings (ET_A) and 7.7 for inhibition of sarafotoxin S6c-induced contractions in rat tracheal rings (ET_B). In *in vivo*, it significantly attenuated the pressor effect of big ET-1 in pithed rats (1-30 mg/kg i.v.) and dose-dependently increased (1-10 mg/kg i.v.) ET-1 plasma concentrations in conscious rats. In spontaneously hypertensive rats, it was as potent as bosentan at the maximal effective dose of 10 mg/kg and more potent than both BQ-123 and BMS-182874 in decreasing arterial blood pressure. Compound (10 mg/kg i.v.) was also able to prevent acute renal failure that complicates rhabdomyolysis in a rat model of myoglobinuric nephropathy. Tezosentan showed good water solubility and has a short half-life after i.v. administration, allowing a plateau effect to be reached rapidly. In a double-blind, placebo-controlled study in healthy volunteers, compound showed a good safety profile, without affecting blood pressure up to the maximum dose tested of 600 mg/kg i.v. over 1 h. Compound was eliminated rapidly, with an apparent elimination half-life of 10 min. Potentially useful for the treatment of acute heart failure and renal failure.

SOURCES – Actelion; Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Novel sulfonamides*. EP 799209, JP 98509182, WO 9619459.

2. Clozel, M. et al. *Pharmacology of tezosentan, new endothelin receptor antagonist designed for parenteral use*. J Pharmacol Exp Ther 1999, 290(2): 840.

3. Clozel, M. et al. *Preclinical and clinical pharmacology of tezosentan, a new endothelin receptor antagonist designed for parenteral use*. 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst O49.

4. Stowe, N.T. et al. *Comparison of pre vs. post ischemic administration of an endothelin receptor antagonist in a rat kidney ischemia/reperfusion model*. 32nd Annu Meet Am Soc Nephrol (Nov 5-8, Miami Beach) 1999, Abst A3614.

5. Torre-Amione, G. et al. *Results of a randomized, placebo-controlled, hemodynamic trial with an intravenous endothelin-1 receptor antagonist in patients with congestive heart failure*. Circulation 1999, 100(18, Suppl, 1): Abst 3410.

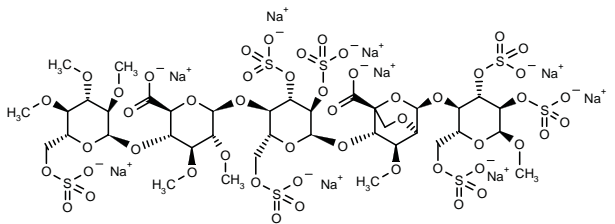
*Identified compound 239527 (see 239030) Drug Data Rep 1996, 018(10): 0881.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

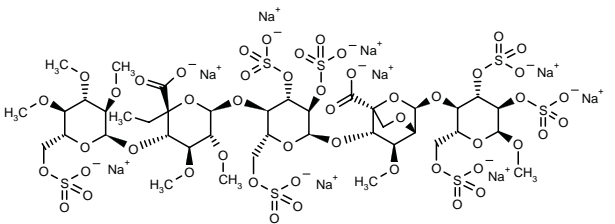
279116

Methyl *O*-(2,3,4-tri-*O*-methyl-6-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,3-di-*O*-methyl- β -D-glucopyranosyluronic acid)-(1 \rightarrow 4)-*O*-(2,3,6-tri-*O*-sulfo- α -D-glucopyranosyl)-(1 \rightarrow 4)-*O*-(2,6-anhydro-5-*C*-carboxy-3-*O*-methyl- α -L-idopyranosyl)-(1 \rightarrow 4)-2,3,6-tri-*O*-sulfo- α -D-glucopyranoside nonasodium salt

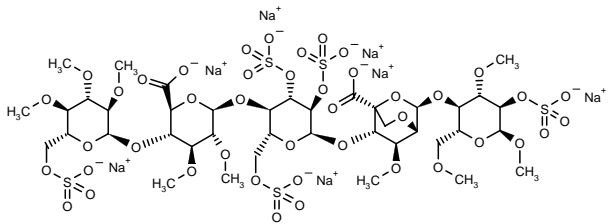


C38 H53 Na9 O49 S7; Mol wt: 1725.1600

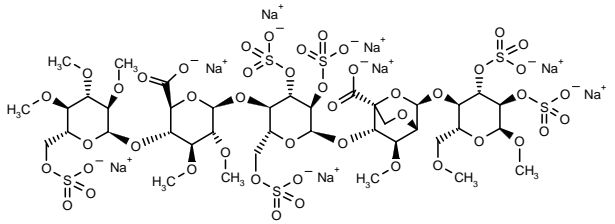
ACTION – Anticoagulant and antithrombotic agent with potent anti-factor Xa activity and high affinity for antithrombin III. Other exemplified compounds from this series of pentasaccharide derivatives include the following:



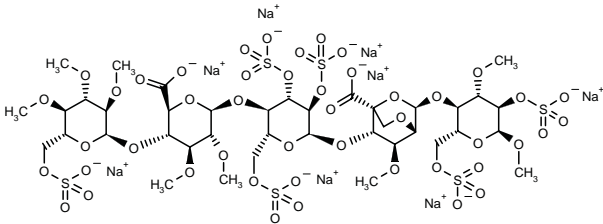
279117: C40 H57 Na9 O49 S7



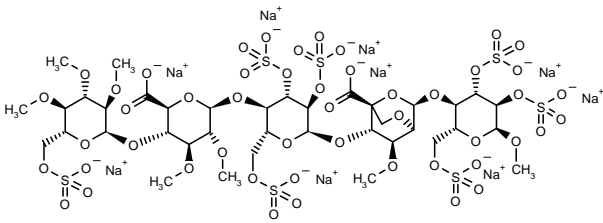
279118: C40 H59 Na7 O43 S5



279119: C39 H56 Na8 O46 S6



279120: C39 H56 Na8 O46 S6



279121: C38 H53 Na9 O49 S7

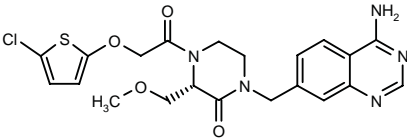
SOURCES – Akzo Nobel; Sanofi-Synthelabo.

REFERENCES

1. Petitou, M. (Sanofi SA;Akzo Nobel N.V.) *New pentasaccharides, their methods of production and pharmaceutical compsns. containing same.* FR 2773801, WO 9936428.

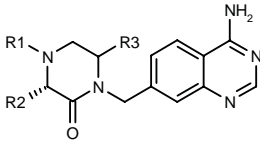
279375

1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)oxyacetyl]-3(*S*)-(methoxymethyl)piperazin-2-one

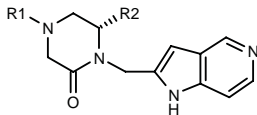


C21 H22 Cl N5 O4 S; Mol wt: 475.9548

ACTION – Anticoagulant and antithrombotic agent with factor Xa-inhibitory activity. Other specifically claimed compounds within this series of substituted oxoaza-heterocyclic derivatives include the following:



Compound	R1	R2	R3	Formula
279376	5-Cl-2-thienyl-OCH2CO	CH2OMe	Me	C ₂₂ H ₂₄ ClN ₅ O ₄ S
279379	5-Cl-2-thienyl-CH=CHCO	CH2OMe	H	C ₂₂ H ₂₂ ClN ₅ O ₃ S
279380	5-Cl-2-thienyl-CH=CHCH2	H	H	C ₂₀ H ₂₀ ClN ₅ OS
279382	6-NH2-3-Pyr-CH=CHCO	Pr	H	C ₂₄ H ₂₇ N ₇ O ₂



Compound	R1	R2	Formula
279377	6-Cl-2-benzothienyl-SO2	H	C ₂₆ H ₁₇ ClN ₄ O ₃ S ₂
279378	5-Cl-2-thienyl-CH=CHSO2	H	C ₁₈ H ₁₇ ClN ₄ O ₃ S ₂
279381	5-Cl-2-thienyl-CH=CHSO2	CH2OH	C ₁₉ H ₁₉ ClN ₄ O ₄ S ₂

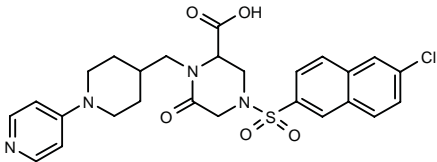
SOURCE – Rhône-Poulenc Rorer.

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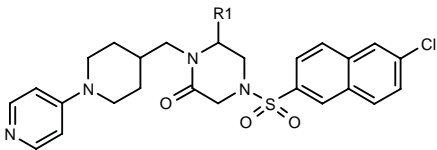
279436

4-(6-Chloro-2-naphthylsulfonyl)-6-oxo-1-[1-(pyridin-4-yl)piperidin-4-ylmethyl]piperazine-2-carboxylic acid



C26 H27 Cl N4 O5 S; Mol wt: 543.0413

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of human factor Xa (IC₅₀ = 0.0074 μM). Compound was also shown to double prothrombin time (PT) in rat plasma at 2.7 μM. Other compounds from this series of cyclic amino derivatives include the following:



Compound	R1	Isomer	Formula
279437	CO2Et		C ₂₈ H ₃₁ ClN ₄ O ₅ S
279438	CONH2		C ₂₆ H ₂₈ ClN ₅ O ₄ S
279439	CH=NOH		C ₂₆ H ₂₈ ClN ₅ O ₄ S
279440	CH2NH2		C ₂₆ H ₃₀ ClN ₅ O ₃ S
279441	CH2N(Me)2		C ₂₈ H ₃₄ ClN ₅ O ₃ S
279442	CH2NHAc	R	C ₂₈ H ₃₂ ClN ₅ O ₄ S
279443	CO2Et	R	C ₂₈ H ₃₁ ClN ₄ O ₅ S

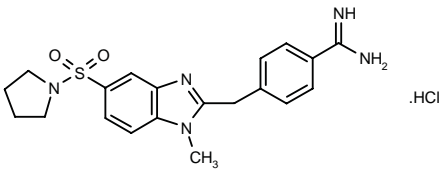
SOURCE – Mochida.

REFERENCES

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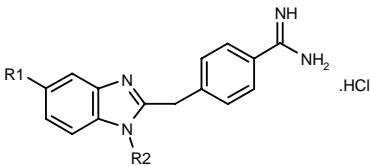
279857

4-[1-Methyl-5-(1-pyrrolidinylsulfonyl)-1H-benzimidazol-2-ylmethyl]benzamidinium hydrochloride

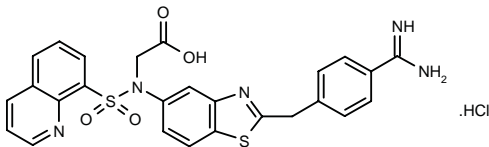


C20 H23 N5 O2 S . HCl; Mol wt: 433.9616

ACTION – Anticoagulant and antithrombotic agent shown to prolong the activated partial thromboplastin time (aPTT) with an ED₂₀₀ value (concentration doubling aPTT) of 0.25 μM. Other representative compounds within this series of 5-membered, benzo-condensed heterocycles with thrombin- and/or factor Xa-inhibitory activity include the following:



Compound	R1	R2	Formula
279859	N(8-quinoliny-SO2)-COCH2NHCH2CO2H	Me	C ₂₇ H ₂₄ N ₆ O ₄ S.HCl
279861	N(8-quinoliny-SO2)-COCH2NHCH2CO2H	Me	C ₂₉ H ₂₇ N ₇ O ₅ S.HCl
279863	N(SO2Ph)CH2-CH2N(Me)2	CH2Ph	C ₃₂ H ₃₄ N ₆ O ₂ S.HCl
279866	N(SO2Ph)CH2-CH2N(Et)2	CH2CONH-CH2CO2H	C ₃₁ H ₃₇ N ₇ O ₅ S.HCl
279867	N(cyclopentyl)SO2Me	Me	C ₂₂ H ₂₇ N ₅ O ₂ S.HCl
279870	N(cyclopentyl)-COCH2CH2CO2H	Me	C ₂₅ H ₂₉ N ₅ O ₃ .HCl
279872	1-(1-pyrrolidiny-CO)-cyclopropyl	Me	C ₂₄ H ₂₇ N ₅ O.HCl



279874: C26 H21 N5 O4 S2 . HCl

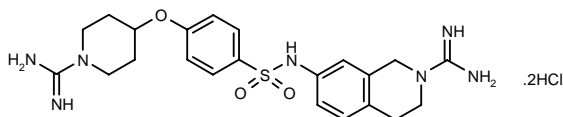
SOURCE – Boehringer Ingelheim.

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280255

7-[4-(1-Amidinopiperidin-4-yloxy)phenylsulfonamido]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide dihydrochloride



C22 H29 N7 O3 S . 2HCl; Mol wt: 544.5049

ACTION – Antithrombotic agent proven to potently inhibit human factor Xa ($K_i = 0.010 \mu\text{M}$) with selectivity relative to thrombin and trypsin ($K_i = 2 \mu\text{M}$ and $0.1 \mu\text{M}$, respectively). Anticoagulant activity was demonstrated in human plasma by its ability to prolong the activated partial thromboplastin time (aPTT) and thrombin time (TT).

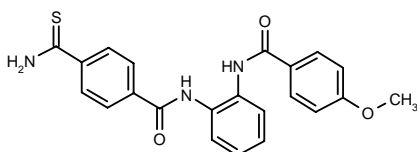
SOURCE – Roche Diagnostics.

REFERENCES

1. Grams, F. et al. (Roche Diagnostics GmbH) *Sulfonamides with antithrombotic activity*. EP 937723, WO 9942462.

280286

N-[2-(4-Methoxybenzamido)phenyl]-4-(thiocarbamoyl)-benzamide



C22 H19 N3 O3 S; Mol wt: 405.4761

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of factor Xa with a K_i of $0.050 \mu\text{M}$; it did not inhibit thrombin or trypsin ($K_i > 100 \mu\text{M}$). Compound concentration-dependently prolonged activated partial thromboplastin time (aPTT) in human plasma. A representative compound from a series of thiobenzamides.

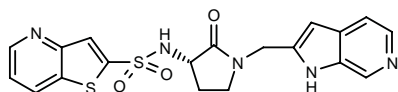
SOURCE – Roche Diagnostics.

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RPR-208707**279528**

N-[2-Oxo-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)methyl]-pyrrolidin-3(*S*)-yl]thieno[3,2-*b*]pyridine-2-sulfonamide



C19 H17 N5 O3 S2; Mol wt: 427.5073

ACTION – Antithrombotic agent, a potent and selective inhibitor of factor Xa ($K_i = 0.018 \mu\text{M}$) with good selectivity with respect to a panel of serine proteases including trypsin, plasmin, tissue plasminogen activator (t-PA), activated protein C (APC) and factor IIa ($K_i > 2.9$, > 7.3 , > 8.7 , > 18 and $> 4 \mu\text{M}$, respectively). In dogs, compound at a dose of 10 mg/kg p.o. showed moderate *ex vivo* anti-factor Xa activity (25% at 2 h) and low plasma concentrations (240 nM).

SOURCE – Rhône-Poulenc Rorer.

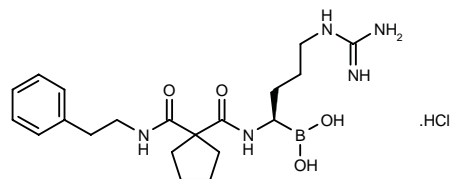
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2. Becker, M.R. et al. *Azaindole pyrrolidinone inhibitors of factor Xa: SAR, synthesis, and X-ray crystal structure of a novel surrogate for basic P1 moieties*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 33.
3. Guilloteau, J.-P. et al. *Crystal structures of human factor Xa complexed with potent inhibitors*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 20.

S-31214***279687**

268769 (as besylate)

1 (*R*)-[1-[*N*-(2-Phenylethyl)carbamoyl]cyclopentyl-carboxamido]-4-guanidinobutylboronic acid hydrochloride



C20 H32 B N5 O4 . HCl; Mol wt: 453.7757

ACTION – Anticoagulant and antithrombotic agent, a potent and selective thrombin inhibitor ($\text{IC}_{50} = 1.8 \text{ nM}$) with moderate to good selectivity against a panel of other serine proteases including trypsin and plasmin ($\text{IC}_{50} = 23$ and 5593 nM , respectively). In dogs, compound given orally at 5 mg/kg exhibited anticoagulant activity, as demonstrated by increases in both the thrombin time and the activated partial thromboplastin time.

SOURCE – Servier.

REFERENCES

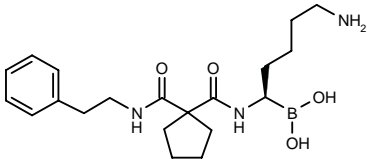
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2. Gloanec, P. et al. *New dicarbonyl cycloalkyl based thrombin inhibitors with improved activity and selectivity compared to (D)-Phe-Pro-boroArg derivatives*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 201.

*Identified compound **268769** (see **268762**) Drug Data Rep 1998, 020(11): 0951.

S-31922

279689

5-Amino-1(*R*)-[1-[*N*-(2-phenylethyl)carbamoyl]cyclopentylcarboxamido]pentylboronic acid



C20 H32 B N3 O4; Mol wt: 389.3008

ACTION – Antithrombotic agent, a potent thrombin inhibitor (IC₅₀ = 43-82 nM) with high selectivity over other serine proteases including trypsin and plasmin (IC₅₀ = 813 and 13,930 nM, respectively). Compound showed good oral bioavailability in dogs (36%) and was able to increase the *ex vivo* activated partial thromboplastin time (aPTT) at doses of 25 mg/kg p.o. and 1 mg/kg i.v.

SOURCE – Servier.

REFERENCES

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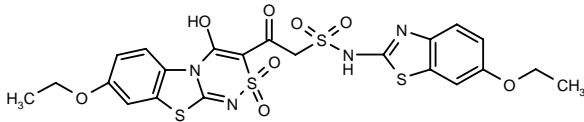
2. Gloanec, P. et al. *New dicarbonyl cycloalkyl based thrombin inhibitors with improved activity and selectivity compared to (D)-Phe-Pro-boroArg derivatives*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 201.

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ANTIPLATELET THERAPY

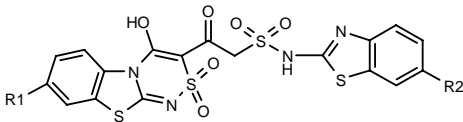
279097

N-(6-Ethoxybenzothiazol-2-yl)-2-(8-ethoxy-4-hydroxy-2,2-dioxo[1,2,4]thiadiazino[3,4-*b*]benzothiazol-3-yl)-2-oxoethane-1-sulfonamide



C22 H20 N4 O8 S4; Mol wt: 596.6840

ACTION – Antithrombotic agent that acts by selectively inhibiting platelet ADP receptors. *In vitro*, it was shown to inhibit ADP-induced aggregation of human platelet-rich plasma (PRP) and the binding of the potent ADP receptor agonist [³H]-2-MeS-ADP to whole human platelets with IC₅₀ values of 0.18 and 0.17 μM, respectively. Compound exhibited about 1000-fold selectivity for ADP receptors relative to other receptors from the P2 family such as the human P2Y₁ receptor, as demonstrated by its lack of activity on 2-MeS-ADP-induced intracellular calcium mobilization in cloned Jurkat cells expressing the hP2Y₁ receptor (IC₅₀ > 100 μM). Other compounds from this series of fused heterocyclic derivatives include the following:



Compound	R1=R2	Formula
279098	SO2Me	C ₂₀ H ₁₆ N ₄ O ₁₀ S ₆
279099	OMe	C ₂₀ H ₁₆ N ₄ O ₈ S ₄

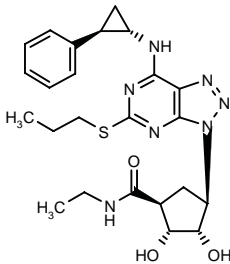
SOURCE – COR Therapeutics.

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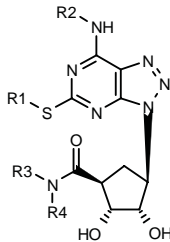
280068

(1*S*,2*R*,3*S*,4*R*)-*N*-Ethyl-2,3-dihydroxy-4-[7-[(1*S*,2*R*)-2-phenylcyclopropylamino]-5-(propylsulfanyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide



C24 H31 N7 O3 S; Mol wt: 497.6209

ACTION – Platelet aggregation inhibitor and antithrombotic agent that acts as a P2T purinoceptor antagonist. Other exemplified compounds from this series of triazolo[4, 5-*d*]pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
280069	Me	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	Et	H	C ₂₂ H ₂₇ N ₇ O ₃ S
280071	Me	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	Ph	H	C ₂₈ H ₂₇ N ₇ O ₃ S
280072	Me	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	cyclopropyl	H	C ₂₃ H ₂₇ N ₇ O ₃ S
280073	Pr	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	CH ₂ CH ₂ F	H	C ₂₄ H ₃₀ FN ₇ O ₃ S
280074	Pr	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	4-F-Ph(CH ₂) ₃	H	C ₃₁ H ₃₆ FN ₇ O ₃ S
280075	Pr	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	4-CF ₃ -Ph(CH ₂) ₃	H	C ₃₂ H ₃₆ F ₃ N ₇ O ₃ S
280076	Pr	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	CH ₂ CH ₂ OMe	Me	C ₂₈ H ₃₅ N ₇ O ₄ S
280077	Pr	(1 <i>S</i> ,2 <i>R</i>)-2-Ph-cyclopropyl	2-Pyr-CH ₂	H	C ₂₈ H ₃₂ N ₈ O ₃ S
280078	Pr	3-Pyr-(CH ₂) ₃	Et	H	C ₂₃ H ₃₂ N ₈ O ₃ S

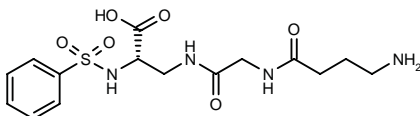
SOURCE – AstraZeneca.

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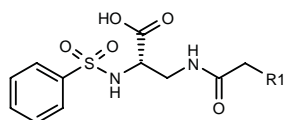
281198

3-[2-(4-Aminobutyramido)acetamido]-2(S)-(phenylsulfonamido)propionic acid



C15 H22 N4 O6 S; Mol wt: 386.4268

ACTION – Fibrinogen (gpIIb/IIIa) receptor antagonist shown to inhibit ADP-induced human platelet aggregation with an IC_{50} of $< 5 \mu M$. Other specifically claimed compounds are:



Compound	R1	Formula
281199	1-Piz-(CH2)3	C ₁₈ H ₂₈ N ₄ O ₅ S
281200	NHCO(CH2)6NH2	C ₁₈ H ₂₈ N ₄ O ₆ S

SOURCE – Merck & Co.

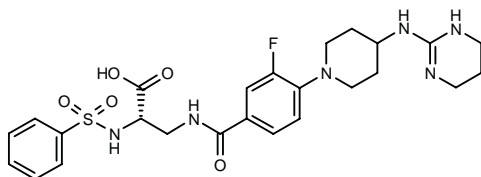
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CP-4632

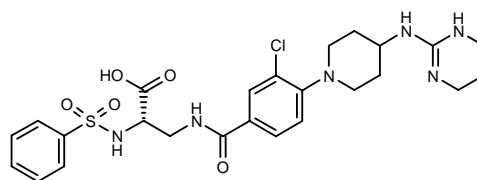
279529

3-[3-Fluoro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-ylamino)piperidin-1-yl]benzamido]-2(S)-(phenylsulfonamido)propionic acid



C25 H31 F N6 O5 S; Mol wt: 546.6209

ACTION – Potent dual integrin $\alpha_v\beta_3$ and fibrinogen gpIIb/IIIa receptor antagonist (IC_{50} = 0.20 and 0.17 nM, respectively); it inhibited $\alpha_v\beta_3$ -mediated cell adhesion in vascular smooth cells from humans, dogs, rats and hamsters (IC_{50} = 37, 1.4, 230 and 730 nM, respectively) and macrophage adhesion to vitronectin. Compound exhibited antiplatelet activity *in vitro* in human and dog platelets (IC_{50} = 55 and 30 nM, respectively) and *ex vivo* in dog platelets (10-30 $\mu g/kg$ i.v.), but did not prolong the bleeding time in dogs. Compound showed acceptable water solubility (1.5 mg/l) and a 34-min half-life in rats after i.v. dosing. Potentially useful for the treatment of acute ischemic diseases. Another related compound is:



CP-4685 [282977]: C25 H31 Cl N6 O5 S

SOURCE – Meiji Seika.

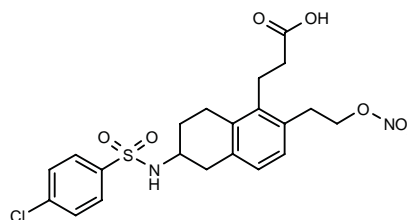
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3. Kubota, D. et al. *Novel integrin $\alpha_v\beta_3$ antagonists as tricyclic pharmacophore based molecules.* 19th Symp Med Chem (Nov 17-19, Tokyo) 1999, Abst 1P-01.

S-31354*

268583

3-[6-(4-Chlorophenylsulfonamido)-2-(2-nitrooxyethyl)-5,6,7,8-tetrahydro-1-naphthyl]propionic acid



C21 H23 Cl N2 O7 S; Mol wt: 482.9387

ACTION – Agent for the treatment of thrombotic and atherosclerotic cardiovascular diseases with antiplatelet and vasodilating effects, a thromboxane receptor (TP) antagonist with nitric oxide (NO) donor properties. In isolated rabbit saphenous vein, compound strongly inhibited U-46619-induced contractions (pA_2 = 9.5) and caused endothelium-independent relaxation of KCl-precontracted preparations (IC_{50} = 2 μM), even in the presence of a guanylyl cyclase inhibitor (IC_{50} = 18 μM). S-31354 was able to inhibit U-46619-induced human platelet aggregation (IC_{50} = 0.14 μM) and to completely prevent ADP-induced rabbit platelet aggregation at 100 μM . In dogs, compound given orally at 1 mg/kg suppressed U-46619-induced *ex vivo* platelet aggregation; it produced a transient decrease in arterial blood pressure in anesthetized rats at 3 mg/kg i.v.

SOURCE – Servier.

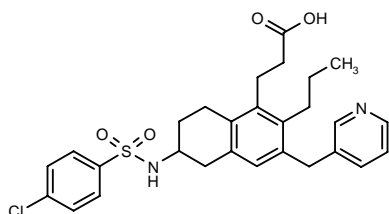
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*Identified compound **268583** Drug Data Rep 1998, 020(11): 0948.

S-32080***264967**

3-[6-(4-Chlorophenylsulfonamido)-2-propyl-3-(3-pyridylmethyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid



C₂₈ H₃₁ Cl N₂ O₄ S; Mol wt: 527.0819

ACTION – Agent for the treatment of cardiovascular diseases related to thrombosis and atherosclerosis, a dual thromboxane receptor (TP) antagonist and thromboxane (TxA₂) synthase inhibitor. *In vitro*, it selectively inhibited U-46619-induced contractions in rabbit saphenous vein (pA₂ = 8.4) and U-46619-induced platelet aggregation (IC₅₀ = 360 nM), as well as TxA₂ production by coagulating human blood (IC₅₀ = 460 nM). In dogs, compound given orally at a dose of 10 mg/kg completely suppressed U-46619-induced *ex vivo* platelet aggregation and induced a long-lasting (24 h) decrease in TxA₂ production (65%) and increase in PGE₂ production in whole blood. In guinea pigs, compound given i.v. inhibited carotid artery thrombosis.

SOURCE – Servier.

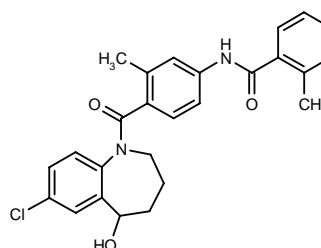
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3. Verbeuren, T.J. et al. *S 32080 is a novel mixed TP-receptor antagonist and TxA₂-synthase inhibitor*. Thromb Haemost 1999, (Suppl.): Abst 1166.

*Identified compound **264967** Drug Data Rep 1998, 020(08): 0683.

RENAL-UROLOGIC DRUGS**DIURETICS****OPC-41061****255241**

N-[4-(7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-ylcarbonyl)-3-methylphenyl]-2-methylbenzamide



C₂₆ H₂₅ Cl N₂ O₃; Mol wt: 448.9475

ACTION – Highly potent, selective, orally active, nonpeptide arginine vasopressin (AVP) V₂ receptor antagonist (K_i = 1.33 and 325 nM for rat V₂ and V_{1a} receptor subtypes, respectively) with high affinity and selectivity for human V₂ receptors (K_i = 0.43, 12.3 and > 100,000 nM, respectively, for V₂, V_{1a} and V_{1b} receptor subtypes). In normally hydrated, conscious rats, at 2 h after dosing, compound increased urine volume (ED₃ [dose required to increase by 3-fold basal urine volume] = 30.54 mg/kg p.o.), decreased urine osmolality and increased serum sodium concentrations. The acute aquaretic effects of OPC-41061 were confirmed after chronic administration (1 and 10 mg/kg/day p.o. for 28 days); no difference in serum osmolality, sodium, creatinine, urea nitrogen and AVP concentrations, nor in pituitary AVP content or AVP receptors in the kidney and liver, was observed throughout the study, indicating that compound is devoid of the side effects (saliuresis) of conventional diuretics. Potentially useful for the treatment of conditions characterized by water retention and the inappropriate secretion of AVP.

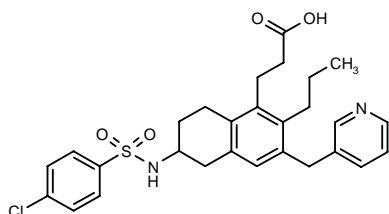
SOURCE – Otsuka.

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S-32080***264967**

3-[6-(4-Chlorophenylsulfonamido)-2-propyl-3-(3-pyridylmethyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid



C28 H31 Cl N2 O4 S; Mol wt: 527.0819

ACTION – Agent for the treatment of cardiovascular diseases related to thrombosis and atherosclerosis, a dual thromboxane receptor (TP) antagonist and thromboxane (TxA₂) synthase inhibitor. *In vitro*, it selectively inhibited U-46619-induced contractions in rabbit saphenous vein (pA₂ = 8.4) and U-46619-induced platelet aggregation (IC₅₀ = 360 nM), as well as TxA₂ production by coagulating human blood (IC₅₀ = 460 nM). In dogs, compound given orally at a dose of 10 mg/kg completely suppressed U-46619-induced *ex vivo* platelet aggregation and induced a long-lasting (24 h) decrease in TxA₂ production (65%) and increase in PGE₂ production in whole blood. In guinea pigs, compound given i.v. inhibited carotid artery thrombosis.

SOURCE – Servier.

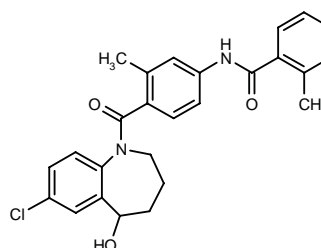
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*Identified compound **264967** Drug Data Rep 1998, 020(08): 0683.

RENAL-UROLOGIC DRUGS**DIURETICS****OPC-41061****255241**

N-[4-(7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-ylcarbonyl)-3-methylphenyl]-2-methylbenzamide



C26 H25 Cl N2 O3; Mol wt: 448.9475

ACTION – Highly potent, selective, orally active, nonpeptide arginine vasopressin (AVP) V₂ receptor antagonist (K_i = 1.33 and 325 nM for rat V₂ and V_{1a} receptor subtypes, respectively) with high affinity and selectivity for human V₂ receptors (K_i = 0.43, 12.3 and > 100,000 nM, respectively, for V₂, V_{1a} and V_{1b} receptor subtypes). In normally hydrated, conscious rats, at 2 h after dosing, compound increased urine volume (ED₃ [dose required to increase by 3-fold basal urine volume] = 30.54 mg/kg p.o.), decreased urine osmolality and increased serum sodium concentrations. The acute aquaretic effects of OPC-41061 were confirmed after chronic administration (1 and 10 mg/kg/day p.o. for 28 days); no difference in serum osmolality, sodium, creatinine, urea nitrogen and AVP concentrations, nor in pituitary AVP content or AVP receptors in the kidney and liver, was observed throughout the study, indicating that compound is devoid of the side effects (saliuresis) of conventional diuretics. Potentially useful for the treatment of conditions characterized by water retention and the inappropriate secretion of AVP.

SOURCE – Otsuka.

REFERENCES

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2. Nakagawa, S. et al. (Otsuka Pharmaceutical Co., Ltd.) *Solid pharmaceutical compsns*. JP 99021241.
3. Ogawa, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Oxytocin antagonist*. EP 602209, JP 94087747, JP 94092854, WO 9401113.
4. Ogawa, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Vasopressin antagonists*. JP 92321669.
5. Yamamura, Y. et al. (Otsuka Pharmaceutical Co., Ltd.) *Agent for prophylaxis or treatment of cataract*. EP 686035, JP 94305968, WO 9418975.
6. Abbas, R. et al. *A sensitive and specific chiral HPLC-MS/MS method for quantitative analysis of R(+) and S(-) enantiomers of OPC-41061 in human serum*. 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 129.

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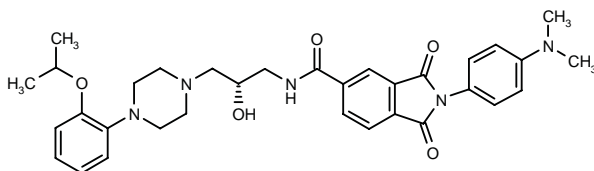
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BENIGN PROSTATIC HYPERPLASIA THERAPY

279916

2-[4-(Dimethylamino)phenyl]-N-[2(S)-hydroxy-3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl]-1,3-dioxo-2,3-dihydro-1H-indole-5-carboxamide



C33 H39 N5 O5; Mol wt: 585.7011

ACTION – Potent α_{1a} -adrenoceptor antagonist ($K_i = 0.33$ nM) with high selectivity over α_{1b} - and α_{1d} -adrenoceptors ($K_i > 2000$ nM), being more selective than the reference α_{1a} -adrenoceptor antagonist tamsulosin ($K_i = 0.13$ nM; 14.8- and 1.4-fold selectivity over α_{1b} - and α_{1d} -adrenoceptors, respectively). Potentially useful for the treatment of benign prostatic hyperplasia.

SOURCE – Ortho-McNeil.

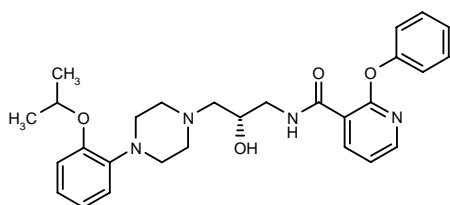
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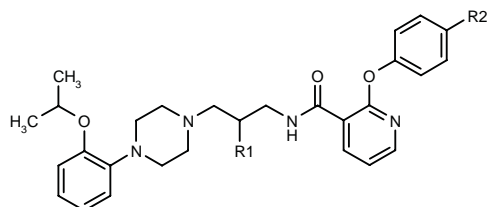
280275

N-[2(S)-Hydroxy-3-[4-(2-isopropoxyphenyl)-1-piperazinyl]propyl]-2-phenoxy pyridine-3-carboxamide



C28 H34 N4 O4; Mol wt: 490.6006

ACTION – Agent for the treatment of benign prostatic hyperplasia that acts as a potent antagonist at α_{1a} -adrenoceptors ($IC_{50} = 0.76$ nM) with much weaker affinity for α_{1b} - and α_{1d} -adrenoceptors ($IC_{50} = 668$ and 81 nM, respectively). Compound exhibits selectivity for prostatic over aortic tissue, as demonstrated *in vivo* by its ability to dose-dependently inhibit phenylephrine (PE)-induced increases in intraurethral pressure in dogs following i.v. administration as compared to its effects on PE-induced increases in arterial pressure. Other compounds from this series of substituted pyridino arylpiperazines include the following:



Compound	R1	R2	Formula
280276	OH	H	C ₂₈ H ₃₄ N ₄ O ₄
280277	H	Me	C ₂₉ H ₃₆ N ₄ O ₃
280278	OH	Me	C ₂₉ H ₃₆ N ₄ O ₄

SOURCE – Ortho-McNeil.

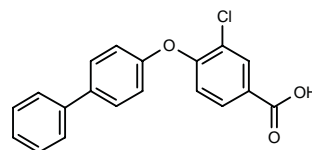
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YM-31758

223464

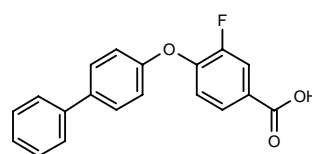
4-(Biphenyl-4-yloxy)-3-chlorobenzoic acid



C19 H13 Cl O3; Mol wt: 324.7617

M.p. 204-5 °C.

ACTION – Human prostatic 5 α -reductase inhibitor ($IC_{50} = 0.87$ nM) with > 1000-fold selectivity over rat enzyme and more potent inhibitory activity than finasteride ($IC_{50} = 4.1$ nM). Potentially useful for the treatment of androgen-related disorders including benign prostatic hyperplasia and skin disorders such as acne and hirsutism. Another compound within this class of phenoxybenzoic acid derivatives is:



223465: C19 H13 F O3

SOURCE – Yamanouchi.

REFERENCES

1. Hara, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Medicine containing benzoic acid deriv. and novel benzoic acid deriv.* JP 93331059, JP 93331104, JP 94183961, JP 95500395, WO 9324442.

2. Igarashi, S. et al. *A novel class of inhibitors for human steroid 5α-reductase: Phenoxybenzoic acid derivatives. I.* Chem Pharm Bull 1999, 47(8): 1073.

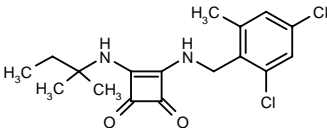
3. Igarashi, S. et al. *Synthesis of new phenoxy benzoate induction and its 5α-reductase inhibitor.* 115th Annu Meet Pharm Soc Jpn (March 29-31, Sendai) 1995, Abst 30 (P1) 13-156.

TREATMENT OF URINARY INCONTINENCE

WAY-151616*1-4

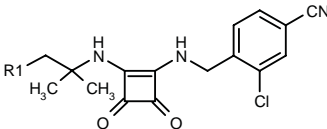
261214

3-(2,4-Dichloro-6-methylbenzylamino)-4-(1,1-dimethyl-propylamino)-3-cyclobutene-1,2-dione



C17 H20 Cl2 N2 O2; Mol wt: 355.2630

ACTION – ATP-sensitive potassium channel opener shown to antagonize KCl-induced contractions of isolated rat bladder detrusor strips (IC₅₀ = 0.097 μM). *In vivo*, compound inhibited abnormal spontaneous contractions in a pathophysiological model of bladder instability in rats with hypertrophied bladder (ED₅₀ = 0.6 mg/kg p.o.) at doses producing minimal hemodynamic changes. Potentially useful for the treatment of bladder instability in urge urinary incontinence. Other representative compounds within this series of cyclobutenediones are:



Compound	R1	Formula
WAY-138351 [261968]**,1-4	H	C ₁₆ H ₁₆ ClN ₃ O ₂
WAY-139799 [261972]***,1,3,4	Me	C ₁₇ H ₁₈ ClN ₃ O ₂

SOURCE – American Home Products.

REFERENCES

1. Antane, M.M. et al. (American Home Products Corp.) *Substd. N-arylmethylamino derivs. of cyclobutene-3,4-diones.* US 5763474, US 5780505, WO 9802413.

2. Gast, M.J. and Koziol, T.R. (American Home Products Corp.) *Method of treating urinary incontinence.* WO 9811888.

3. Antane, M.M. et al. *Design and SAR of novel potassium channel openers targeted for urge urinary incontinence.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 17.

4. McFarlane, G.R. et al. *Benzylamino analogs of 1,2-diaminocyclobutene-3,4-dione as novel KATP-channel openers targeted for treatment of urge urinary incontinence.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 35.

*Identified compound **261214** Drug Data Rep 1998, 020(05): 0411.

Identified compound **261968 (see **261214**) Drug Data Rep 1998, 020(05): 0411.

***Identified compound **261972** (see **261214**) Drug Data Rep 1998, 020(05): 0411.

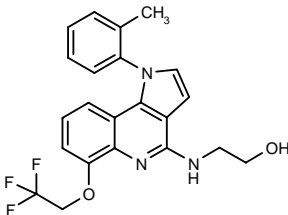
GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

AU-413*1,2

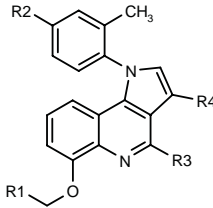
274003

2-[1-(2-Methylphenyl)-6-(2,2,2-trifluoroethoxy)-1H-pyr-rolo[3,2-c]quinolin-4-ylamino]ethanol



C22 H20 F3 N3 O2; Mol wt: 415.4130

ACTION – Antiulcer agent, a proton pump (H⁺/K⁺-ATPase) inhibitor (IC₅₀ = 8.1 and 34.6 μM, respectively, against enzyme from hog and rabbit gastric microsomes) with potency comparable to omeprazole (IC₅₀ = 9.6 and 22.4 μM, respectively). In rats, it inhibited both basal and histamine-stimulated gastric acid secretion (ED₅₀ = 7.1 and 28 mg/kg i.d., respectively) and protected from gastric damage induced by ethanol and NaOH (ED₅₀ = 12 and 41 mg/kg p.o., respectively). Other compounds within this series of acylquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
AU-090 [279192]	H	i-BuCOO	H	Me	C ₂₅ H ₂₆ N ₂ O ₃
AU-091 [279193]	H	i-BuOCO	H	Me	C ₂₅ H ₂₆ N ₂ O ₄
AU-254 [279194]	H	H	H	Me	C ₂₀ H ₁₈ N ₂ O
AU-466 [279195]	CF3	OMe	NHMe	H	C ₂₂ H ₂₀ F ₃ N ₃ O ₂

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *Pyrrolo[3,2-c]-quinoline derivs. containing haloalkoxy group and pharmaceutically acceptable salts thereof.* CA 2268166, WO 9909029.

2. Cheon, H.G. et al. *Anti-ulcer activity of newly synthesized acylquinoline derivatives.* Arch Pharmacol Res 1999, 22(2): 137.

REFERENCES

1. Hara, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Medicine containing benzoic acid deriv. and novel benzoic acid deriv.* JP 93331059, JP 93331104, JP 94183961, JP 95500395, WO 9324442.

2. Igarashi, S. et al. *A novel class of inhibitors for human steroid 5 α -reductase: Phenoxybenzoic acid derivatives. I.* Chem Pharm Bull 1999, 47(8): 1073.

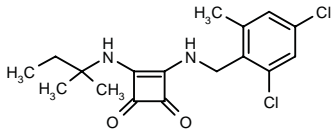
3. Igarashi, S. et al. *Synthesis of new phenoxy benzoate induction and its 5 α -reductase inhibitor.* 115th Annu Meet Pharm Soc Jpn (March 29-31, Sendai) 1995, Abst 30 (P1) 13-156.

TREATMENT OF URINARY INCONTINENCE

WAY-151616*1-4

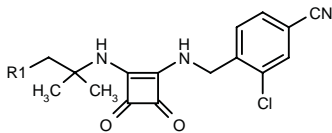
261214

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C17 H20 Cl2 N2 O2; Mol wt: 355.2630

ACTION – ATP-sensitive potassium channel opener shown to antagonize KCl-induced contractions of isolated rat bladder detrusor strips (IC₅₀ = 0.097 μ M). *In vivo*, compound inhibited abnormal spontaneous contractions in a pathophysiological model of bladder instability in rats with hypertrophied bladder (ED₅₀ = 0.6 mg/kg p.o.) at doses producing minimal hemodynamic changes. Potentially useful for the treatment of bladder instability in urge urinary incontinence. Other representative compounds within this series of cyclobutenediones are:



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SOURCE – American Home Products.

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3. Antane, M.M. et al. *Design and SAR of novel potassium channel openers targeted for urge urinary incontinence.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 17.

4. McFarlane, G.R. et al. *Benzylamino analogs of 1,2-diaminocyclobutene-3,4-dione as novel KATP-channel openers targeted for treatment of urge urinary incontinence.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 35.

*Identified compound **261214** Drug Data Rep 1998, 020(05): 0411.

Identified compound **261968 (see **261214**) Drug Data Rep 1998, 020(05): 0411.

***Identified compound **261972** (see **261214**) Drug Data Rep 1998, 020(05): 0411.

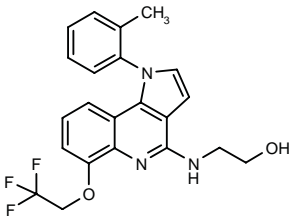
GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

AU-413*1,2

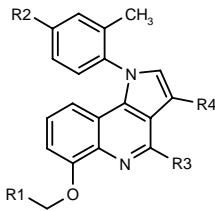
274003

2-[1-(2-Methylphenyl)-6-(2,2,2-trifluoroethoxy)-1H-pyr-rolo[3,2-c]quinolin-4-ylamino]ethanol



C22 H20 F3 N3 O2; Mol wt: 415.4130

ACTION – Antiulcer agent, a proton pump (H⁺/K⁺-ATPase) inhibitor (IC₅₀ = 8.1 and 34.6 μ M, respectively, against enzyme from hog and rabbit gastric microsomes) with potency comparable to omeprazole (IC₅₀ = 9.6 and 22.4 μ M, respectively). In rats, it inhibited both basal and histamine-stimulated gastric acid secretion (ED₅₀ = 7.1 and 28 mg/kg i.d., respectively) and protected from gastric damage induced by ethanol and NaOH (ED₅₀ = 12 and 41 mg/kg p.o., respectively). Other compounds within this series of acylquinoline derivatives include the following:



Compound	R1	R2	R3	R4	Formula
AU-090 [279192]	H	i-BuCOO	H	Me	C ₂₅ H ₂₆ N ₂ O ₃
AU-091 [279193]	H	i-BuOCOO	H	Me	C ₂₅ H ₂₆ N ₂ O ₄
AU-254 [279194]	H	H	H	Me	C ₂₀ H ₁₈ N ₂ O
AU-466 [279195]	CF3	OMe	NHMe	H	C ₂₂ H ₂₀ F ₃ N ₃ O ₂

SOURCE – Korea Research Institute of Chemical Technology, Taejon (KR).

REFERENCES

1. Choi, J.-K. et al. (Korea Research Institute of Chemical Technology) *Pyrrolo[3,2-c]-quinoline derivs. containing haloalkoxy group and pharmaceutically acceptable salts thereof.* CA 2268166, WO 9909029.

2. Cheon, H.G. et al. *Anti-ulcer activity of newly synthesized acylquinoline derivatives.* Arch Pharmacol Res 1999, 22(2): 137.

3. Yum, E.K. et al. *Synthesis and pharmacological profile of 1-aryl-3-substituted pyrrolo[3,2-c]quinolones*. Bioorg Med Chem Lett 1999, 9(19): 2819.

*Identified compound **274003** (see **273995**) Drug Data Rep 1999, 021(05): 0424.

INFLAMMATORY BOWEL DISEASE THERAPY

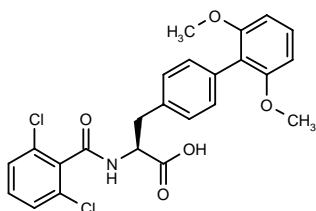
TR-14035

278989

2(S)-(2,6-Dichlorobenzamido)-3-(2',6'-dimethoxybiphenyl-4-yl)propionic acid

N-(2,6-Dichlorobenzoyl)-3-(2',6'-dimethoxybiphenyl-4-yl)-L-alanine

N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine



C24 H21 Cl2 N O5; Mol wt: 474.3379

ACTION – Dual $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrin antagonist, (IC_{50} = 5 and 46 nM, respectively) with high selectivity over other integrins including $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_1\beta_1$, $\alpha_v\beta_3$, $\alpha_L\beta_2$ and $\alpha_E\beta_7$ (IC_{50} >10 μ M). Compound showed similar potency in inhibiting CS-1, MAdCAM, VCAM and [125 I]-MAdCAM binding to $\alpha_4\beta_7$ (IC_{50} = 5, 13, 19 and 2.1 nM, respectively). At doses of 10-30 mg/kg p.o., it was active in several *in vivo* models of inflammation including a model of arthritis and delayed-type hypersensitivity. Compound showed a favorable pharmacokinetic profile, with oral absorption of 60% in rats and 25% in dogs and a plasma half-life of 5 h in rats and 2.6 h in dogs. Selected for preclinical development in the treatment of disorders such as inflammatory bowel disease, asthma, diabetes and rheumatoid arthritis.

SOURCE – Tanabe Seiyaku.

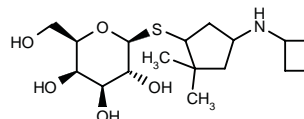
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1. Sircar, I. et al. (Tanabe Seiyaku Co., Ltd.) *Inhibitors of α_4 mediated cell adhesion*. WO 9936393.
2. Martin, R. et al. *SAR of TR-14035: An orally active dual $\alpha_4\beta_7/\alpha_4\beta_1$ integrin antagonist*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 60.
3. Sircar, I. et al. *Discovery of TR-14035: An orally active dual $\alpha_4\beta_7/\alpha_4\beta_1$ integrin antagonist*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 59.

ANTIDIARRHEAL AGENTS

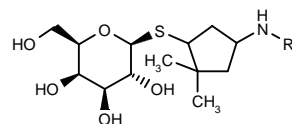
280196

1-Deoxy-1-[4-(cyclobutylamino)-2,2-dimethylcyclopent-1-ylsulfanyl]- β -D-galactopyranose



C17 H31 N O5 S; Mol wt: 361.4999

ACTION – An inhibitor of the binding of toxins such as heat-labile enterotoxin (LT) and cholera toxin (CT) to their receptors, also reported to inhibit the binding of certain organisms such as *Vibrio cholerae* and enterotoxigenic strains of *Escherichia coli* to their cell-surface receptors. Potentially useful for the treatment of diseases caused by toxins such as diarrhea including traveller's diarrhea and cholera. Other specifically claimed compounds from this series of 1-galactose derivatives include the following:



Compound	R1	Formula
280197	3,3-(Me)2-cyclobutyl	C ₁₉ H ₃₅ NO ₅ S
280198	cyclopentyl	C ₁₈ H ₃₃ NO ₅ S
280199	3-Me-cyclopentyl	C ₁₉ H ₃₅ NO ₅ S
280200	3,3-(Me)2-cyclopentyl	C ₂₀ H ₃₇ NO ₅ S
280201	cyclohexyl	C ₁₉ H ₃₅ NO ₅ S
280202	3-Me-cyclohexyl	C ₂₀ H ₃₇ NO ₅ S
280203	4-Me-cyclohexyl	C ₂₀ H ₃₇ NO ₅ S

SOURCE – Synsorb Biotech.

REFERENCES

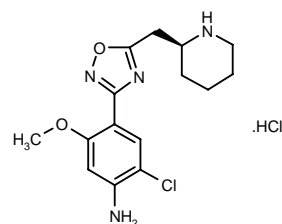
1. Hindsgaul, O. (Synsorb Biotech Inc.) *1-Galactose derivs*. EP 938492, US 5932554.

AGENTS FOR CONSTIPATION

YM-53389

278142

(+)-2-Chloro-5-methoxy-4-[5-[piperidin-2(S)-ylmethyl]-1,2,4-oxadiazol-3-yl]phenylamine monohydrochloride



C15 H19 Cl N4 O2 . HCl; Mol wt: 359.2550

M.p. 217-8 °C, $[\alpha]_D^{20} +14.9^\circ$ (*c* 1.00, MeOH).

ACTION – 5-HT₄ receptor agonist with nanomolar affinity for human receptors ($K_i = 54$ nM) and no affinity for 5-HT_{1A}, 5-HT₂ and 5-HT₃ receptors, α - and β -adrenoceptors, muscarinic, dopaminergic, histaminic, adenosine, opiate, CCK, angiotensin II, neurokinin NK₁ or neuro-peptide Y receptors ($K_i > 10,000$ nM); cisapride and other benzamides such as renzapride and zacopride showed, in contrast, a potent interaction with 5-HT₃ receptors. Compound exhibited potent agonist activity, similar to cisapride, in guinea pig ileum longitudinal muscle myenteric plexus preparations ($EC_{50} = 0.5$ μ M) and in rat esophagus ($pEC_{50} = 6.3$), and had negligible 5-HT₃ receptor-antagonist activity. *In vivo*, at doses of 1-10 mg/kg s.c. it shortened whole-gut transit time in mice but did not significantly affect upper gastrointestinal propulsion. Potentially useful for the treatment of gastrointestinal disorders associated with reduced intestinal propulsion such as constipation.

SOURCE – Yamanouchi.

REFERENCES

1. Suzuki, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Oxadiazole derivs. and medicinal compsn. thereof*. WO 9532965.

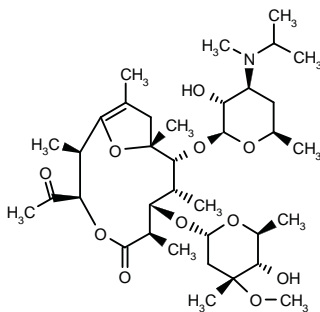
2. Nagakura, Y. et al. *Pharmacological properties of a novel gastrointestinal prokinetic benzamide selective for human 5-HT₄ receptor versus human 5-HT₃ receptor*. Pharmacol Res 1999, 39(5): 375.

3. Suzuki, T. et al. *Synthesis of the selective 5-hydroxytryptamine 4 (5-HT₄) receptor agonist (+)-(S)-2-chloro-5-methoxy-4-[5-(2-piperidylmethyl)-1,2,4-oxadiazol-3-yl]aniline*. Chem Pharm Bull 1999, 47(1): 120.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

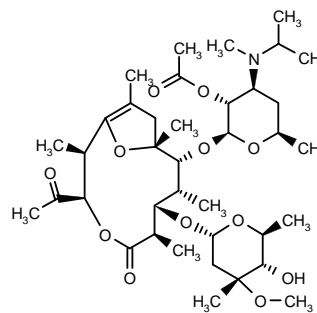
280253

(2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-3-Acetyl-7-(2,6-didesoxy-3-*C*-methyl-3-*O*-methyl- α -L-ribohexopyranosyloxy)-9-[3-(*N*-isopropyl-*N*-methylamino)-3,4,6-tridesoxy- β -D-xylohexopyranosyloxy]-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one



C36 H61 N O11; Mol wt: 683.8739

ACTION – Gastric prokinetic agent, a derivative of erythromycin A with motilin receptor-agonist activity ($pIC_{50} = 8.01$ in a binding assay using [¹²⁵I]-motilin as the ligand) but devoid of antibacterial activity. Compound was shown to have excellent bioavailability and oral efficacy in dogs. Another exemplified compound is:



280254: C38 H63 N O12

SOURCE – Solvay.

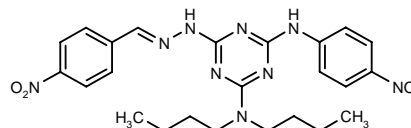
REFERENCES

1. Jasserand, D. et al. (Solvay Pharmaceuticals GmbH) *11-Acetyl-12,13-dioxabicyclo-[8.2.1]tridecenone derivs., process for making them and pharmaceutical compsns. containing them*. CA 2260315, DE 19805822, EP 937734, JP 99269193.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

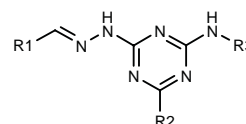
279070

4-Nitrobenzaldehyde *N*-[4-(dibutylamino)-6-(4-nitrophenylamino)-1,3,5-triazin-2-yl]hydrazone



C24 H29 N9 O4; Mol wt: 507.5521

ACTION – Antiviral agent particularly useful for the treatment of hepatitis B virus (HBV) infections that acts by inhibiting viral replication by binding and inhibiting functional nucleic acids; in particular, compound is reported to specifically recognize an essential and multifunctional RNA structure of the HBV pregenomic RNA known as encapsidation signal (ϵ RNA). *In vitro*, compound was active against HBV in infected 2.2.15 cells ($EC_{50} = 0.411$ μ M, $EC_{90} = 1.2$ μ M), while showing no cytotoxicity ($CC_{50} = 307$ μ M). In addition, it exhibited a strong synergistic effect when combined with the antiviral agent 3TC (lamivudine) at a molar ratio of 15:1. In a nucleic acid binding assay, it was shown to concentration-dependently bind to labeled ϵ RNA. Other compounds from this series of triazine derivatives include the following:



Compound	R1	R2	R3	Formula
279071	2-Me-3-indolyl	NHPh	4-NO ₂ -Ph	C ₂₅ H ₂₁ N ₉ O ₂
279072	4-Me-Ph	2-Me-PhNH	4-NO ₂ -Ph	C ₂₄ H ₂₂ N ₈ O ₂
279073	5-Br-2-MeO-Ph	4-morpholinyl	3-NO ₂ -Ph	C ₂₁ H ₂₁ BrN ₈ O ₄
279074	2-OH-5-I-Ph	Ph	CH ₂ Ph	C ₂₃ H ₂₀ IN ₇ O
279075	2,4-(MeO)2-Ph	NHPh	2,4-(Me)2-Ph	C ₂₆ H ₂₇ N ₇ O ₂

SOURCE – Scriptgen.

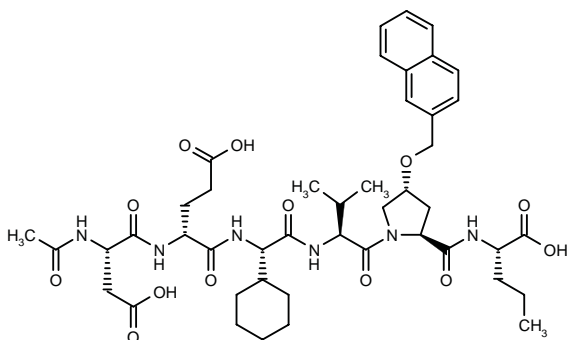
REFERENCES

1. Arenas, J.E. et al. (Scriptgen Pharmaceuticals, Inc.) *Triazine antiviral cpds.* WO 9936410.

BILN-303-SE

279688

Acetyl-L-aspartyl-D-glutamyl-L-(2-cyclohexyl)glycyl-L-valyl-4(*R*)-(2-naphthylmethoxy)-L-prolyl-L-norvaline



C45 H62 N6 O13; Mol wt: 895.0138

ACTION – Antiviral agent, a competitive inhibitor of hepatitis C virus NS3 protease complexed with the NS4A peptide cofactor (NS3-4Apep protease; $K_i = 3$ nM) with more than 100,000-fold selectivity over other proteases including chymotrypsin, porcine pancreatic elastase, cathepsin B, human leukocyte elastase and human cytomegalovirus proteases.

SOURCE – Boehringer Ingelheim.

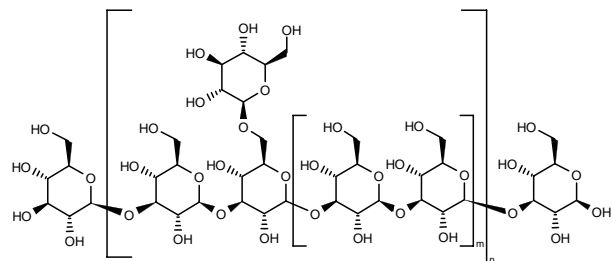
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2. Ghiri, E. *Peptide-based inhibitors of the hepatitis C virus serine protease.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 276.

G009

246402

β -(1 \rightarrow 3)-Glucan with β -(1 \rightarrow 6) side-chain isolated from the *Basidiomycetes Ganoderma lucidum*



ACTION – Hepatoprotectant and immunostimulant isolated from the mushroom *Ganoderma lucidum* IY009, proven to have hepatoprotective effects in several animal models including experimental hepatitis or liver toxicity

induced by acetaminophen, galactosamine or CCl_4 , where it was able to decrease blood GOT (ALT) and GTP (AST) levels, restore liver tissue histology to normal and suppress lipid peroxidation. Compound also exhibited antifibrotic effect in rats with experimental hepatic cirrhosis by decreasing hydroxyproline content in liver tissue, suppressing blood stasis and inflammation and improving bile duct proliferation and liver fibrosis. It was shown to stimulate NO production by macrophages by inducing NOS gene expression. Compound also exerts antitumor activity via activation of the immune system and showed anticarcinogenic effects in an *in vivo* model of carcinogenesis. A phase I clinical trial demonstrated good tolerance and phase II clinical studies are in progress.

SOURCE – Il-Yang.

REFERENCES

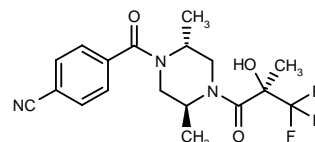
1. Lee, K.H. et al. (Il-Yang Pharmaceutical Co., Ltd.) *Ganoderma lucidum IY009 which produces proteoglycan (G009) having effect of enhancing antitumor immunity.* US 5721134, WO 9210562.
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 6. Momose, Y. and Shigematsu, A. *Radiorespirometric patterns of [^{14}C]-substrates in rats. II. Differences with the nature and administration route of the injection fluid.* Eur J Drug Metab Pharmacokinet 1991, 16(1): 35.
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 8. Park, E.J. et al. *The antifibrotic effects of polysaccharides extract from Ganoderma lucidum on the experimental hepatic cirrhosis.* Yakhak Hoeji 1994, 38(3): 338.
- MONOGRAPH** – Baek, S.-J. et al. *G009.* Drugs Fut 1999, 24(10): 1068.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

279489

4-[2(*R*),5(*S*)-Dimethyl-4-[3,3,3-trifluoro-2(*R*)-hydroxy-2-methylpropionyl]piperazin-1-ylcarbonyl]benzonitrile



C18 H20 F3 N3 O3; Mol wt: 383.3680

M.p. 172-5 °C.

SOURCE – Scriptgen.

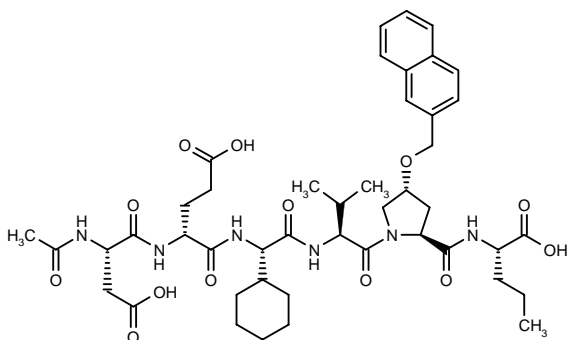
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BILN-303-SE

279688

Acetyl-L-aspartyl-D-glutamyl-L-(2-cyclohexyl)glycyl-L-valyl-4(*R*)-(2-naphthylmethoxy)-L-prolyl-L-norvaline



C45 H62 N6 O13; Mol wt: 895.0138

ACTION – Antiviral agent, a competitive inhibitor of hepatitis C virus NS3 protease complexed with the NS4A peptide cofactor (NS3-4Apep protease; $K_i = 3$ nM) with more than 100,000-fold selectivity over other proteases including chymotrypsin, porcine pancreatic elastase, cathepsin B, human leukocyte elastase and human cytomegalovirus proteases.

SOURCE – Boehringer Ingelheim.

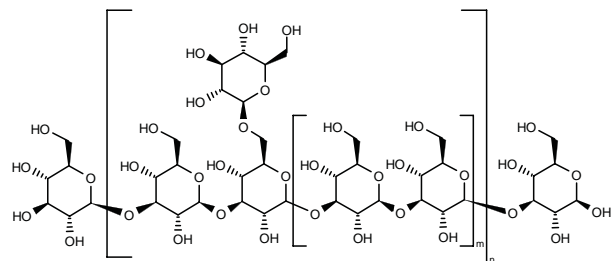
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G009

246402

β -(1 \rightarrow 3)-Glucan with β -(1 \rightarrow 6) side-chain isolated from the *Basidiomycetes Ganoderma lucidum*



ACTION – Hepatoprotectant and immunostimulant isolated from the mushroom *Ganoderma lucidum* IY009, proven to have hepatoprotective effects in several animal models including experimental hepatitis or liver toxicity

induced by acetaminophen, galactosamine or CCl_4 , where it was able to decrease blood GOT (ALT) and GTP (AST) levels, restore liver tissue histology to normal and suppress lipid peroxidation. Compound also exhibited antifibrotic effect in rats with experimental hepatic cirrhosis by decreasing hydroxyproline content in liver tissue, suppressing blood stasis and inflammation and improving bile duct proliferation and liver fibrosis. It was shown to stimulate NO production by macrophages by inducing NOS gene expression. Compound also exerts antitumor activity via activation of the immune system and showed anticarcinogenic effects in an *in vivo* model of carcinogenesis. A phase I clinical trial demonstrated good tolerance and phase II clinical studies are in progress.

SOURCE – Il-Yang.

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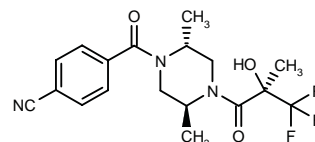
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 8. Park, E.J. et al. *The antifibrotic effects of polysaccharides extract from Ganoderma lucidum on the experimental hepatic cirrhosis.* Yakhak Hoeji 1994, 38(3): 338.
- MONOGRAPH** – Baek, S.-J. et al. *G009.* Drugs Fut 1999, 24(10): 1068.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

279489

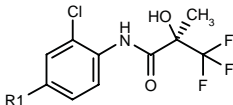
4-[2(*R*),5(*S*)-Dimethyl-4-[3,3,3-trifluoro-2(*R*)-hydroxy-2-methylpropionyl]piperazin-1-ylcarbonyl]benzonitrile



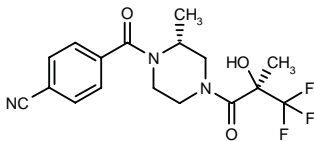
C18 H20 F3 N3 O3; Mol wt: 383.3680

M.p. 172-5 °C.

ACTION – Agent for the treatment of type II diabetes, ischemia, endotoxic and hemorrhagic shock, as well as lactic acidosis and cardiac insufficiency, a potent and orally available inhibitor of pyruvate dehydrogenase kinase (IC_{50} = 16.5 nM) with high selectivity over other eukaryotic serine, threonine and tyrosine protein kinases including cAMP kinase and p38 MAP kinase (IC_{50} > 100 μ M). Compound was able to increase lactate oxidation in a cellular assay (IC_{50} = 57 nM) and to significantly lower blood lactate levels in fasted rats (89% decrease at 1 μ mol/kg p.o.). Other exemplified compounds include the following:



Compound	R1	Formula
279482	CO2H	C ₁₁ H ₉ ClF ₃ NO ₄
279483	1-Piz-SO2	C ₁₄ H ₁₇ ClF ₃ N ₃ O ₄ S



279487: C17 H18 F3 N3 O3

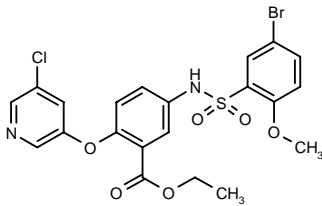
SOURCE – Novartis.

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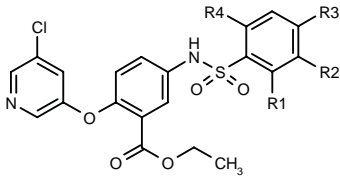
279658

5-(5-Bromo-2-methoxyphenylsulfonamido)-2-(5-chloro-pyridin-3-yloxy)benzoic acid ethyl ester



C21 H18 Br Cl N2 O6 S; Mol wt: 541.8042

ACTION – Peroxisome proliferator-activated receptor PPAR γ modulator (IC_{50} = 0.15 μ M for inhibition of [³H]-BRL-49653 binding) with potential in the treatment of non-insulin-dependent diabetes mellitus (NIDDM), obesity and inflammatory disorders. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
279659	H	OMe	OMe	H	C ₂₂ H ₂₁ ClN ₂ O ₇ S
279660	H	NO2	H	Me	C ₂₁ H ₁₈ ClN ₂ O ₇ S
279661	Cl	H	H	Cl	C ₂₀ H ₁₅ Cl ₃ N ₂ O ₅ S
279662	Cl	H	Cl	Me	C ₂₁ H ₁₇ Cl ₃ N ₂ O ₅ S

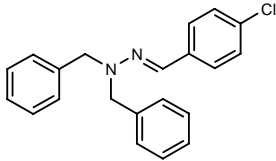
SOURCE – Tularik.

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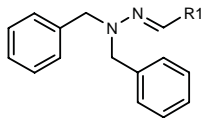
279827

4-Chlorobenzaldehyde N,N-dibenzylhydrazone



C21 H19 Cl N2; Mol wt: 334.8481

ACTION – Agent for the treatment of diseases related to glucose metabolic pathways, particularly hyperglycemia and non-insulin-dependent diabetes mellitus (NIDDM), that acts by inhibiting glucose-6-phosphatases. Other compounds from this series of hydrazone derivatives include the following:



Compound	R1	Formula
279828	5-Et-2-furyl	C ₂₁ H ₂₂ N ₂ O
279829	4-Pyr	C ₂₀ H ₁₉ N ₃
279830	4-MeO-Ph	C ₂₂ H ₂₂ N ₂ O
279832	4-OH-Ph	C ₂₁ H ₂₀ N ₂ O

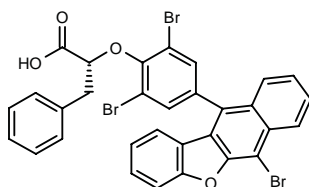
SOURCE – Novo Nordisk.

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279992

2(R)-[2,6-Dibromo-4-(6-bromobenzo[b]naphtho[2,3-d]-furan-11-yl)phenoxy]-3-phenylpropionic acid



C31 H19 Br3 O4; Mol wt: 695.1991

ACTION – Antidiabetic agent, an inhibitor of protein-tyrosine-phosphatase (PTPase) PTP1B (IC_{50} = 83 nM) with more than 25-fold selectivity over other human PTPases including PTP α , PTP1C, CD45 and PTP-PEST. In the *ob/ob* mouse model, compound given orally for 4 days was able to lower plasma glucose (29 and 42%, respectively) and insulin (69 and 86%, respectively) at doses of 10 and 25 mg/kg/day.

SOURCE – Wyeth-Ayerst.

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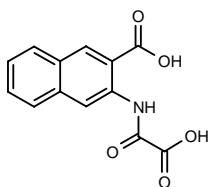
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281203

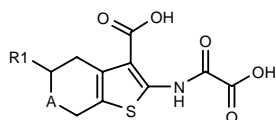
N-(3-Carboxy-2-naphthyl)oxamic acid

3-(Oxaloamino)naphthalene-2-carboxylic acid

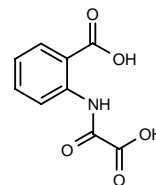


C13 H9 N O5; Mol wt: 259.2161

ACTION – An inhibitor of protein-tyrosine-phosphatases (PTPase) such as PTP1B, with potential in the treatment of a broad range of conditions such as autoimmune diseases, acute and chronic inflammation, osteoporosis, cancer and diabetes, preferably diabetes and related disorders. Other exemplified compounds include the following:



Compound	R1	A	Formula
281206	H	CH2	C ₁₁ H ₁₁ NO ₅ S
281208	1,3-dioxo-2-isoindoliny-CH2	O	C ₁₉ H ₁₄ N ₂ O ₈ S



281205: C9 H7 N O5

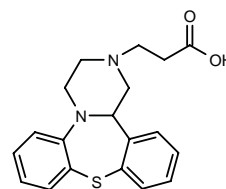
SOURCES – Novo Nordisk; Ontogen.

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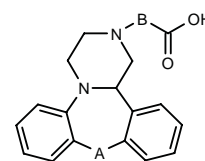
281209

3-(2,3,4,14b-Tetrahydro-1H-dibenzo[b,f]pyrazino[1,2-d]-[1,4]thiazepin-2-yl)propionic acid



C19 H20 N2 O2 S; Mol wt: 340.4450

ACTION – Agent for the treatment of painful, hyperalgesic and/or inflammatory conditions in which C fibers play a role such as neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis that acts by inhibiting the release of neuropeptides from peripheral and central endings of sensory C fibers. Compound also inhibits the release of insulin-antagonizing peptides such as CGRP and amylin from peripheral nerve endings and is thus expected to be useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) and age-associated obesity. *In vivo*, compound was shown to inhibit histamine-induced hyperglycemia in mice (48% inhibition at 1.0 mg/kg i.p.). It is also reported to inhibit histamine-induced paw edema and to improve glucose tolerance in animal models. Within this series of tricyclic compounds, the following are also specifically claimed:



Compound	A	B	Formula
281210	O	-(CH2)3-	C ₂₀ H ₂₂ N ₂ O ₃
281211	S	-(CH2)3-	C ₂₀ H ₂₂ N ₂ O ₂ S
281212	S	-(CH2)4-	C ₂₁ H ₂₄ N ₂ O ₂ S
281213	O	-(CH2)4-	C ₂₁ H ₂₄ N ₂ O ₃
281214	O	-(CH2)2-	C ₁₉ H ₂₀ N ₂ O ₃

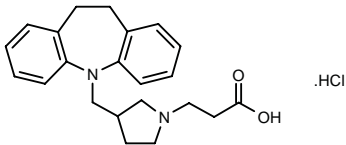
SOURCE – Novo Nordisk.

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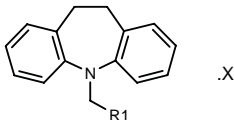
281239

3-[3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-ylmethyl)-pyrrolidin-1-yl]propionic acid hydrochloride



C22 H26 N2 O2 . HCl; Mol wt: 386.9203

ACTION – Agent for the treatment of painful, hyperalgesic and/or inflammatory conditions in which C fibers play a role such as neurogenic pain, neurogenic inflammation, migraine, neuropathy, itching and rheumatoid arthritis that acts by inhibiting the release of neuropeptides from peripheral and central endings of sensory C fibers. Compound also inhibits the release of insulin-antagonizing peptides such as CGRP and amylin from peripheral nerve endings and is thus expected to be useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) and age-associated obesity. *In vivo*, compound was shown to inhibit histamine-induced paw edema in rats (56% inhibition at 1.0 mg/kg i.p.). It is also reported to lower glucose levels and to improve glucose tolerance in diabetic *ob/ob* mice following i.p. administration. Within this series of tricyclic compounds, the following are also specifically claimed:



Compound	R1	X	Formula
281240	4-(CH2CO2H)-2-morpholinyl	oxalate	C ₂₁ H ₂₄ N ₂ O ₃ ·C ₂ H ₄ O ₄
281241	1-(CH2CO2H)-3-Pip	acetate	C ₂₂ H ₂₆ N ₂ O ₂ ·C ₂ H ₄ O ₂
281242	1-(CH2CO2H)-2-Pip-CH2CH2	HCl	C ₂₄ H ₃₀ N ₂ O ₂ ·HCl
281243	1-(CH2CH2CO2H)-4-Pip	oxalate	C ₂₃ H ₂₈ N ₂ O ₂ ·C ₂ H ₂ O ₄

SOURCE – Novo Nordisk.

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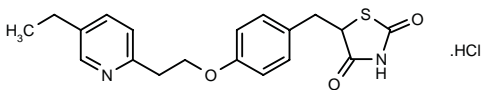
PIOGLITAZONE+ HYDROCHLORIDE

Rec INN; USAN

164965

(±)-5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione monohydrochloride

AD-4833 (free base)
U-72107A



C19 H20 N2 O3 S . HCl; Mol wt: 392.9049

ACTION – Oral antidiabetic agent, a thiazolidinedione that acts mainly by decreasing insulin resistance.

INDICATION – Improvement in glycemic control in patients with type II diabetes as monotherapy or in combination with sulfonylureas, metformin or insulin.

PRESENTATION – Tablets, equivalent to 15, 30 and 45 mg pioglitazone.

PROPRIETARY NAME – Actos (US).

SOURCES – Takeda; comarketed by Lilly.

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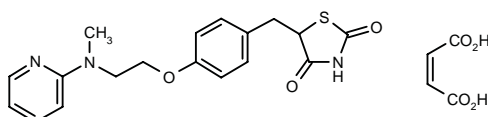
ROSIGLITAZONE MALEATE

Prop INNM

210057

(±)-5-[4-[2-[N-Methyl-N-(2-pyridyl)amino]ethoxy]benzyl]-thiazolidine-2,4-dione maleate

BRL-49653C⁺



C18 H19 N3 O3 S . C4 H4 O4; Mol wt: 473.5037

Free base, white solid, m.p. 153-5 °C.

ACTION – Oral antidiabetic agent, a thiazolidinedione that acts mainly by increasing insulin sensitivity.

INDICATION – Adjunct to diet and exercise for improving glycemic control in patients with type II diabetes, or in combination with metformin.

PRESENTATION – Tablets, equivalent to 2, 4 and 8 mg rosiglitazone.

PROPRIETARY NAME – *Avandia* (US).

SOURCES – SmithKline Beecham; comarketed by Bristol-Myers Squibb.

RECENT REFERENCES

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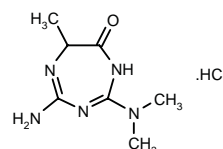
MONOGRAPH – Sorbera, L.A. et al. *Rosiglitazone maleate*. Drugs Fut 1998, 23(9): 0977.

*Drug Data Rep 1994, 016(08): 0744.

TREATMENT OF DIABETIC COMPLICATIONS

278961

2-Amino-4-(dimethylamino)-7-methyl-6,7-dihydro-5H-1,3,5-triazepin-6-one hydrochloride



C7 H13 N5 O . HCl; Mol wt: 219.6746

ACTION – Agent for the treatment or prevention of diabetes and diabetic complications that acts by inhibiting the formation of advanced glycosylation endproducts (AGEs).

SOURCE – Merck KGaA.

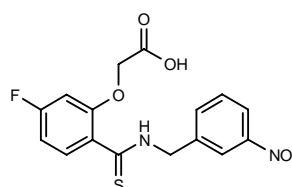
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IDD-598

279597

2-[5-Fluoro-2-[N-(3-nitrobenzyl)thiocarbamoyl]phenoxy]-acetic acid



C16 H13 F N2 O5 S; Mol wt: 364.3517

ACTION – Potent aldose reductase inhibitor (IC_{50} = 6 nM) with 5600-fold selectivity over aldehyde reductase (hALR1; IC_{50} = 35,000 nM). In a model of streptozotocin-induced diabetes in rat, compound at a dose of 50 mg/kg/day p.o. for 4 days lowered sciatic nerve sorbitol levels by 89%. Potentially useful for the treatment of chronic diabetic complications.

SOURCE – Institute for Diabetes Discovery, Branford, CT (US).

REFERENCES

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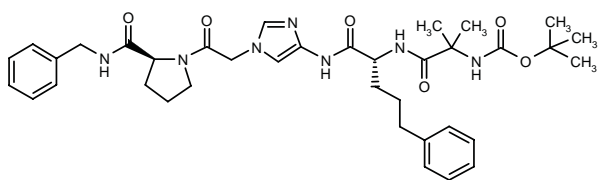
TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

LY-438434¹⁻³

279848

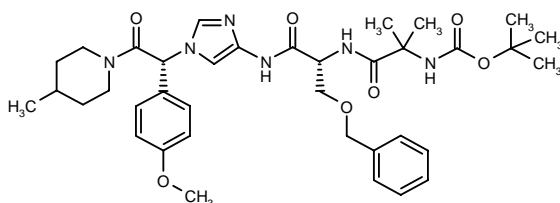
N-[1,1-Dimethyl-2-oxo-2-[2-oxo-2-[1-[2-oxo-2-[2(*S*)-(N-benzylcarbamoyl)pyrrolidin-1-yl]ethyl]-1*H*-imidazol-4-ylamino]-1(*R*)-(3-phenylpropyl)ethylamino]ethyl]carbamic acid *tert*-butyl ester

N-(*tert*-Butoxycarbonyl)-2-methylalanyl-5-phenyl-D-norvalyl-4-amino-1*H*-imidazol-1-ylacetyl-*N*¹-benzyl-L-prolinamide



C37 H49 N7 O6; Mol wt: 687.8371

ACTION – Growth hormone secretagogue whose GH release-stimulating activity was determined *in vitro* in isolated rat pituitary cells (IC₅₀ = 1.9 nM); it is reported to be orally active in dogs. Another representative peptidomimetic imidazole is:



LY-426410 [279491]¹⁻⁴; C37 H50 N6 O7

SOURCE – Lilly.

REFERENCES

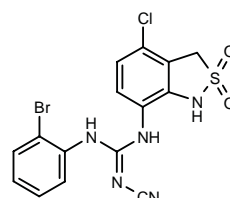
1. Dodge, J.A. et al. (Eli Lilly and Company) *Growth hormone secretagogues*. EP 933365, WO 9908699.
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3. Cohen, J.D. et al. *Design, synthesis, and SAR of novel imidazole-based growth hormone secretagogues*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 131.
4. Muehl, B.S. et al. *Structure-activity relationships of novel imidazole-based growth hormone secretagogues: Modification of the aryl glycine core*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 134.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

278986

*N*¹-(2-Bromophenyl)-*N*³-(4-chloro-2,2-dioxo-2,3-dihydro-1*H*-2,1-benzisothiazol-7-yl)-*N*²-cyanoguanidine



C15 H11 Br Cl N5 O2 S; Mol wt: 440.7079

ACTION – IL-8 (CXCR1 or CXCR2) receptor antagonist with potential in the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, transplant rejection, malaria, restenosis, angiogenesis, rhinovirus infections, periodontal disease or bone resorption disorders.

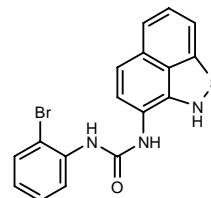
SOURCE – SmithKline Beecham.

REFERENCES

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278987

N-(2-Bromophenyl)-*N*'-(2*H*-naphtho[1,8-*cd*]isothiazol-3-yl)urea



C17 H12 Br N3 O S; Mol wt: 386.2718

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist with potential in the treatment of IL-8-mediated diseases such as asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), psoriasis, arthritis, inflammatory bowel disease, atopic dermatitis, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, transplant rejection, malaria, restenosis, angiogenesis, rhinovirus infections, periodontal disease or bone resorption disorders.

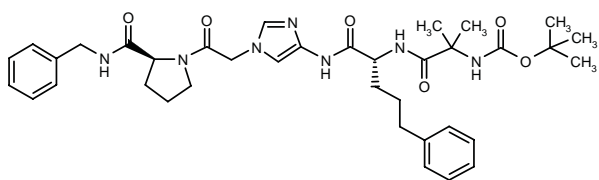
TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

LY-438434¹⁻³

279848

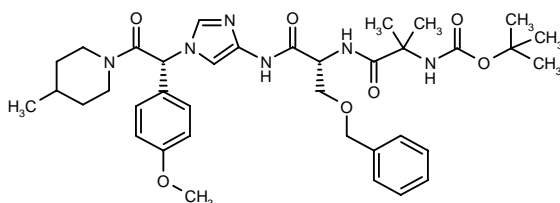
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N-(*tert*-Butoxycarbonyl)-2-methylalanyl-5-phenyl-D-norvalyl-4-amino-1*H*-imidazol-1-ylacetyl-*N*¹-benzyl-L-prolinamide



C37 H49 N7 O6; Mol wt: 687.8371

ACTION – Growth hormone secretagogue whose GH release-stimulating activity was determined *in vitro* in isolated rat pituitary cells (IC₅₀ = 1.9 nM); it is reported to be orally active in dogs. Another representative peptidomimetic imidazole is:



LY-426410 [279491]¹⁻⁴; C37 H50 N6 O7

SOURCE – Lilly.

REFERENCES

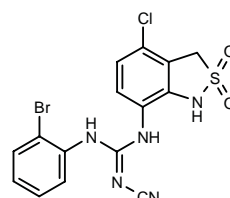
1. Dodge, J.A. et al. (Eli Lilly and Company) *Growth hormone secretagogues*. EP 933365, WO 9908699.
2. Kauffman, R.F. and Palkowitz, A.D. (Eli Lilly and Company) *Treatment of congestive heart failure with growth hormone secretagogues*. WO 9908697.
3. Cohen, J.D. et al. *Design, synthesis, and SAR of novel imidazole-based growth hormone secretagogues*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 131.
4. Muehl, B.S. et al. *Structure-activity relationships of novel imidazole-based growth hormone secretagogues: Modification of the aryl glycine core*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 134.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

278986

*N*¹-(2-Bromophenyl)-*N*³-(4-chloro-2,2-dioxo-2,3-dihydro-1*H*-2,1-benzisothiazol-7-yl)-*N*²-cyanoguanidine



C15 H11 Br Cl N5 O2 S; Mol wt: 440.7079

ACTION – IL-8 (CXCR1 or CXCR2) receptor antagonist with potential in the treatment of IL-8-mediated diseases such as psoriasis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), arthritis, inflammatory bowel disease, atopic dermatitis, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, transplant rejection, malaria, restenosis, angiogenesis, rhinovirus infections, periodontal disease or bone resorption disorders.

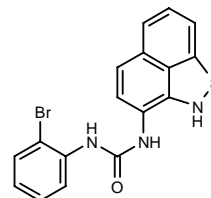
SOURCE – SmithKline Beecham.

REFERENCES

1. Bryan, D.L. and Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9936069.

278987

N-(2-Bromophenyl)-*N*'-(2*H*-naphtho[1,8-*cd*]isothiazol-3-yl)urea



C17 H12 Br N3 O S; Mol wt: 386.2718

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist with potential in the treatment of IL-8-mediated diseases such as asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), psoriasis, arthritis, inflammatory bowel disease, atopic dermatitis, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, transplant rejection, malaria, restenosis, angiogenesis, rhinovirus infections, periodontal disease or bone resorption disorders.

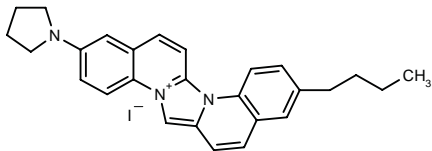
SOURCE – SmithKline Beecham.

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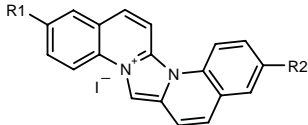
280268

10-Butyl-3-(1-pyrrolidinyl)imidazol[1,2-*a*;3,4-*a'*]diquinoln-15-ylum iodide



C27 H28 I N3; Mol wt: 521.4392

ACTION – IL-8 (CXCR1 or CXCR2) receptor antagonist with potential in the treatment of psoriasis, atopic dermatitis, cancer, asthma, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, septic shock, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease and transplant rejection. *In vitro*, it inhibited rhIL-8-stimulated chemotaxis and calcium flux response of human neutrophils with IC₅₀ values of 0.075 and 0.9 μM, respectively. Within this series of substituted imidazo-[1,2-*a*;3,4-*a'*]diquinolinylium derivatives, the following are also included:



Compound	R1	R2	Formula
280269	1-Pip	Bu	C ₂₈ H ₃₀ I N ₃
280270	t-Bu	1-pyrrolidinyl	C ₂₇ H ₂₈ I N ₃
280271	Bu	N(Me)2	C ₂₆ H ₂₆ I N ₃

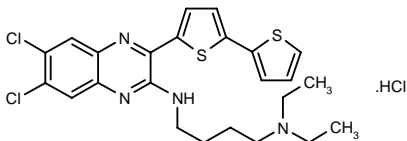
SOURCE – Warner-Lambert.

REFERENCES

1. Low, J.E. and Trivedi, B.K. (Warner-Lambert Co.) *Subst. imidazo[1,2-*a*;3,4-*a'*]diquinolinylium interleukin-8 receptor antagonists*. WO 9942464.

280348

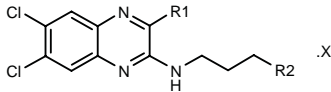
*N*¹-[6,7-Dichloro-3-[5-(2-thienyl)thien-2-yl]quinoxalin-2-yl]-*N*⁴,*N*⁴-diethylbutane-1,4-diamine hydrochloride



C24 H26 Cl2 N4 S2 . HCl; Mol wt: 541.9963

ACTION – IL-8 (CXCR1 or CXCR2) receptor antagonist that inhibits cytokine binding to CXCR1 or CXCR2 receptors. It exhibited potent inhibition of IL-8-stimulated chemotaxis of human neutrophils (IC₅₀ = 0.08 μM). Potentially useful for the treatment of chemokine-

mediated diseases including psoriasis, atopic dermatitis, cancer, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, gastric ulcer, septic shock, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, graft-versus-host reaction, allograft rejection and allergic diseases. Other exemplified substituted quinoxaline derivatives are:



Compound	R1	R2	X	Formula
280349	2-furyl	N(Me)2	HCl	C ₁₇ H ₁₆ Cl ₂ N ₄ O.HCl
280350	2-thienyl	N(Me)2	HCl	C ₁₇ H ₁₆ Cl ₂ N ₄ S.HCl
280351	2-benzothienyl	CH2N(Et)2		C ₂₄ H ₂₆ Cl ₂ N ₄ S
280352	5-Me-2-thienyl	CH2N(Et)2		C ₂₁ H ₂₆ Cl ₂ N ₄ S

SOURCE – Warner-Lambert.

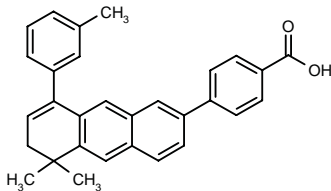
REFERENCES

1. Carson, K.G. et al. (Warner-Lambert Co.) *Subst. quinoxaline derivs. as interleukin-8 receptor antagonists*. WO 9942461, WO 9942463.

BMS-297208

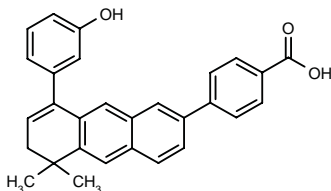
279484

4-[5,5-Dimethyl-8-(3-methylphenyl)-5,6-dihydro-2-anthracenyl]benzoic acid



C30 H26 O2; Mol wt: 418.5334

ACTION – Potent and selective retinoic acid receptor (RAR) antagonist with high functional selectivity for RARγ over RARα and RARβ subtypes (IC₅₀ = 50, 510 and 1830 nM, respectively), as demonstrated by the ability to inhibit the transactivation mediated by *all-trans*-retinoic acid; compound showed nanomolar binding affinity for all three RAR subtypes (K_d = 3.0, 1.6 and 1.2 nM for RARα, RARβ and RARγ, respectively) and was devoid of agonist activity. Potentially useful for the treatment of chronic inflammatory skin disorders such as psoriasis, acne and atopic dermatitis, as well as skin cancer and other neoplasias. Another compound from this series of 8-aryl retinoids is:



BMS-282594 [279485]: C29 H24 O3

SOURCE – Bristol-Myers Squibb.

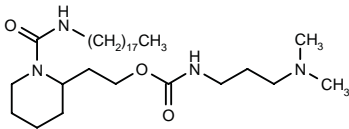
REFERENCES

1. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Retinoid-like cpds.* WO 9849136.
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HAIR GROWTH STIMULANTS

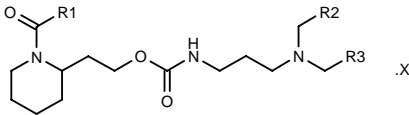
280130

N-[3-(Dimethylamino)propyl]carbamic acid 2-[1-(*N*-octadecylcarbamoyl)-2-piperidinyl]ethyl ester



C32 H64 N4 O3; Mol wt: 552.8826

ACTION – Topical hair growth promoter proven to stimulate 100% regrowth of hair on the backs of mice within 18 days of hair removal when applied at a concentration of 0.1% w/v daily throughout the experiment. Other compounds from this series of 1,2-disubstituted piperidine derivatives include the following:



Compound	R1	R2	R3	X	Formula
280131	NHC18H37	-CH2OCH2-			C ₃₄ H ₆₆ N ₄ O ₄
280132	C17H35	H	H		C ₃₁ H ₆₁ N ₃ O ₃
280133	C17H35	H	H	HCl	C ₃₁ H ₆₁ N ₃ O ₃ ·HCl
280134	C17H35	-CH2OCH2-			C ₃₃ H ₆₃ N ₃ O ₄
280135	C17H35	-CH2OCH2-		HCl	C ₃₃ H ₆₃ N ₃ O ₄ ·HCl
280136	OC18H37	H	H		C ₃₂ H ₆₃ N ₃ O ₄

SOURCE – Shiseido.

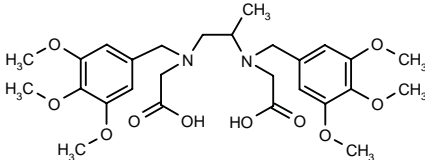
REFERENCES

1. Kobayashi, K. et al. (Shiseido Co. Ltd.) *1,2-Di-substd. piperidine derivs. as hair growth promoter.* EP 933361.

OTHER DERMATOLOGIC DRUGS

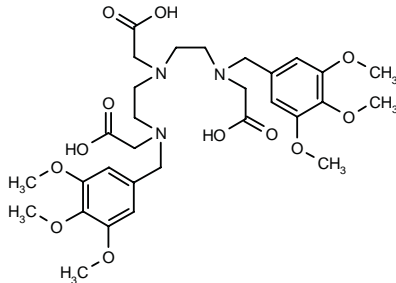
279298

3,6-Bis(3,4,5-trimethoxybenzyl)-4-methyl-3,6-diaza-octanedioic acid

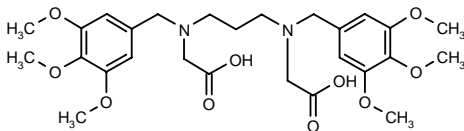


C27 H38 N2 O10; Mol wt: 550.6012

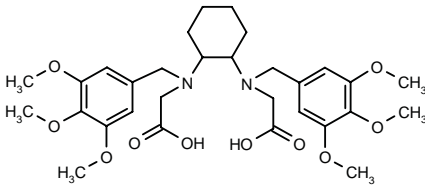
ACTION – Antioxidant with improved solubility as compared to structurally similar agents, for use in pharmaceutical and cosmetic compositions for the relief of oxidative stress in pathological conditions such as aging, cancer, inflammation, ischemia–reperfusion disorders and UV irradiation damage. Other compounds from this series of *N,N'*-di(carboxyalkyl)alkylene di- or triamine derivatives include the following:



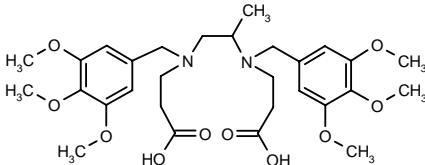
279299:C30 H43 N3 O12



279300: C27 H38 N2 O10



279301: C38 H56 N2 O10



279302: C29 H42 N2 O10

SOURCE – L'Oreal.

REFERENCES

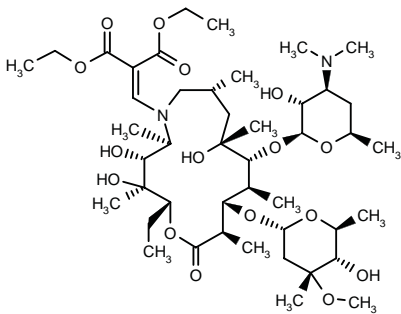
1. Genard, S. and Galey, J.-B. (L'Oreal) *Derivs. of N,N'-di(carboxyalkyl)alkylene di- or triamine.* US 5929112.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

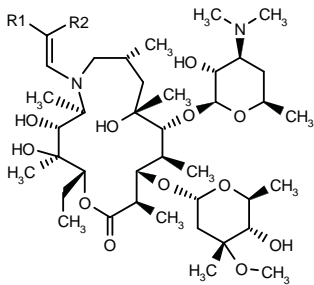
278807

9a-Aza-9-deoxo-9a-*N*-[2,2-di(ethoxycarbonyl)vinyl]-9a-homoerythromycin A



C45 H80 N2 O16; Mol wt: 905.1250

ACTION – Semisynthetic macrolide antibiotic, a derivative of erythromycin A reported to possess comparable efficacy against Gram-positive bacteria while being more effective than erythromycin A against Gram-negative bacteria and clinical isolates. Compound is reported to possess more favorable stability under acidic conditions and lower acute toxicity than erythromycin oxime. Other compounds from this series of β,β-disubstituted derivatives of 9-deoxo-9a-*N*-ethenyl-9a-aza-9a-homoerythromycin A include the following:



Compound	R1	R2	Formula
278808	CN	CO2Et	C ₄₃ H ₇₅ N ₃ O ₁₄
278809	CN	CN	C ₄₁ H ₇₀ N ₄ O ₁₂
278810	Ac	CO2Et	C ₄₄ H ₇₈ N ₂ O ₁₅

SOURCE – Pliva.

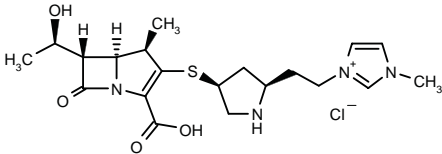
REFERENCES

1. Kujundzic, N. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) β,β-Disubst. derivs. of 9-deoxo-9a-*N*-ethenyl-9a-aza-9a-homoerythromycin A. CA 2256017, EP 927722, JP 99255793.

FR-20950*

203476

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[2(*R*)-[2-(3-methyl-3*H*-imidazol-1-iumyl)ethyl]pyrrolidin-4(*S*)-ylsulfanyl]-1-carbapen-2-em-3-carboxylic acid chloride



C20 H29 Cl N4 O4 S; Mol wt: 456.9960

ACTION – Carbapenem antibiotic active *in vitro* against both Gram-positive and Gram-negative bacteria including methicillin-sensitive *Staphylococcus aureus* 209P JC-1 (MIC < 0.025 µg/ml), methicillin-resistant *S. aureus* 2538 and 3004 (MIC = 1.56 and 12.5 µg/ml, respectively), *Escherichia coli* NIHJ JC-2 (MIC = 0.1 µg/ml), *Proteus vulgaris* IAM 1025 (MIC = 0.78 µg/ml) and *Pseudomonas aeruginosa* strains (MIC = 0.39-1.56 µg/ml). In *P. aeruginosa*-infected mice, compound exhibited protective activity comparable to biapenem, imipenem and meropenem (ED₅₀ = 0.289, 0.289, 0.289 and 0.219 mg/kg s.c., respectively).

SOURCE – Fujisawa.

REFERENCES

1. Chiba, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) 3-Pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid cpds. JP 93239058.

2. Murata, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) Subst. 3-pyrrolidinylthio-carbapenems as antimicrobial agents. EP 636133, JP 95505650, WO 9321186.

3. Azami, H. et al. Synthesis and antibacterial activity of novel 4-pyrrolidinylthio carbapenems. Part III: Novel 2-alkyl substituents containing cationic heteroaromatics linked via a C-N bond. Bioorg Med Chem 1999, 7(8): 1665.

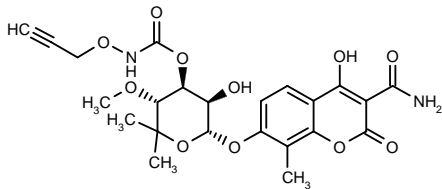
*Identified compound 203476 Drug Data Rep 1994, 016(03): 0284.

ANTIBACTERIAL DRUGS

278868

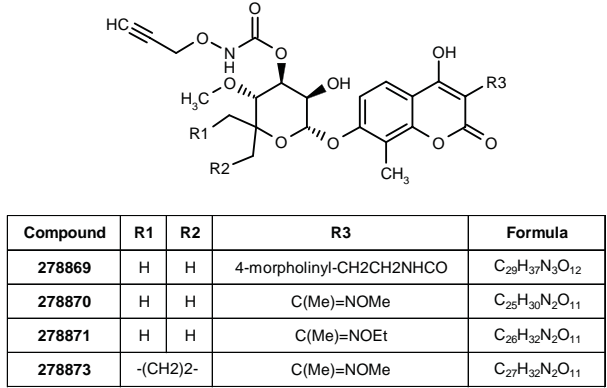
2-Propynyloxycarbamic acid 6(*R*)-[3-carbamoyl-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-7-yloxy]-5(*R*)-hydroxy-3(*R*)-methoxy-2,2-dimethyltetrahydro-2*H*-pyran-4(*S*)-yl ester

7-[6-Deoxy-4-*O*,5-*C*-dimethyl-3-*O*-[*N*-(2-propynyloxy)carbamoyl]-α-*L*-mannopyranosyloxy]-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-3-carboxamide



C23 H26 N2 O11; Mol wt: 506.4614

ACTION – Antibacterial agent active against Gram-positive bacteria, with potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011HT18 (MIC = 0.04 µg/ml), *Staphylococcus epidermidis* 0126042 (MIC = 0.04 µg/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.6 µg/ml), *Streptococcus pneumoniae* 030BI2 (MIC = 0.04 µg/ml), *Enterococcus faecium* 02D3IP2 (MIC = 0.08 µg/ml) and *Enterococcus faecalis* 02D2UC5 (MIC = 0.3 µg/ml) that acts by inhibiting DNA gyrase B (IC₅₀ < 5 µg/ml). Other compounds from this series of aromatic amides include the following:



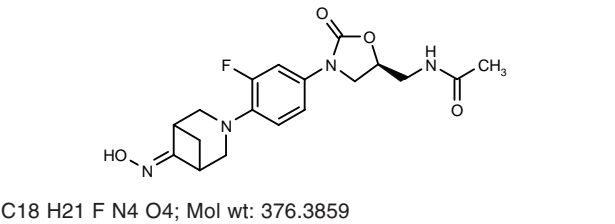
SOURCE – Hoechst Marion Roussel.

REFERENCES

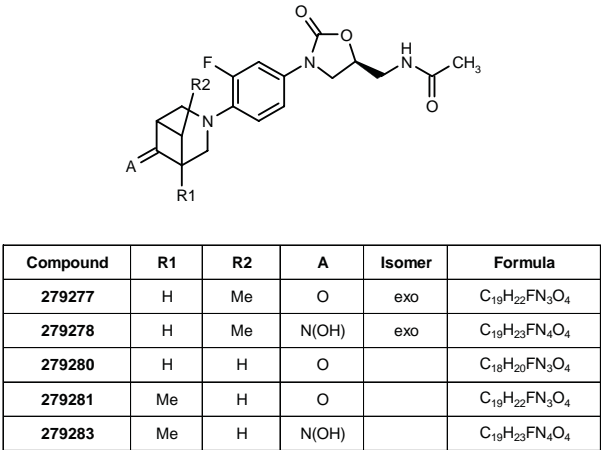
1. Haesslein, J.-L. et al. (Hoechst Marion Roussel, SA) *Novel aromatic amides, preparation method and application as medicines*. FR 2773369, WO 9935155.

279276

N-[3-[3-Fluoro-4-[6-(hydroxyimino)-3-azabicyclo[3.1.1]-hept-3-yl]]phenyl]-2-oxooxazolidin-5(S)-ylmethyl]-acetamide



ACTION – Oxazolidinone antibacterial agent reported to be active against Gram-positive bacteria such as staphylococci, streptococci and enterococci, as well as anaerobic microorganisms such as *Clostridium* spp. and acid-fast microorganisms such as *Mycobacterium* spp. *In vitro*, it exhibited MIC values of 1.00, 1.00, 0.50, 0.50, 0.50 and 0.25 µg/ml against *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* C6068, *Staphylococcus epidermidis* ATCC 12228, *Enterococcus faecium* C 2252, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pyogenes* ATCC 8668, respectively, with comparable or higher potency than vancomycin (MIC = 1.00, 1.00, 1.00, 4.00, 2.00 and 0.50 µg/ml, respectively) and U-100766 (MIC = 2.00, 1.00, 0.50, 2.00, 2.00 and 1.00 µg/ml, respectively). Other specifically claimed compounds from this series of oxazolidinone derivatives include the following:



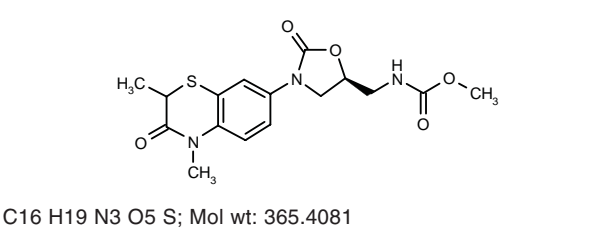
SOURCE – Cheil Jedang.

REFERENCES

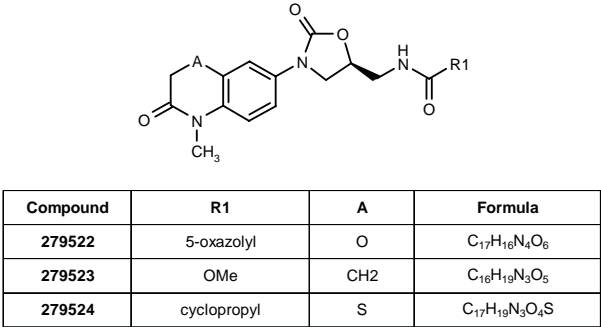
1. Yoon, Y.H. et al. (Cheil Jedang Corporation) *Oxazolidinone derivs. and a method for the preparation thereof and an antibacterial compsn. containing the same*. US 5929083.

279521

N-[3-(2,4-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-7-yl)-2-oxooxazolidin-5(S)-ylmethyl]carbamic acid methyl ester



ACTION – Oxazolidinone antibacterial agent with low toxicity and a broad spectrum of activity against Gram-positive bacteria such as *Staphylococcus aureus* strain 133 (MIC = 1 µg/ml) and *Streptococcus pneumoniae* SP665 (MIC = 2 µg/ml), as well as mycobacteria such as *Mycobacterium smegmatis* DSM 43465 (MIC = 1 µg/ml), *Haemophilus influenzae* and anaerobes. Other compounds from this series of bicyclic-substituted oxazolidinones include the following:



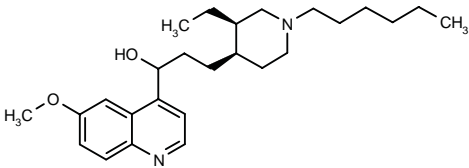
SOURCE – Bayer.

REFERENCES

1. Bartel, S. et al. (Bayer AG) *Novel bicyclic-substd. oxazolidinones*. DE 19802239, WO 9937641.

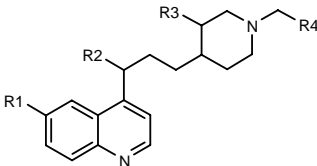
279598

3-[3(*R*)-Ethyl-1-hexylpiperidin-4(*R*)-yl]-1-(6-methoxy-quinolin-4-yl)propan-1-ol



C26 H40 N2 O2; Mol wt: 412.6140

ACTION – Antibacterial agent more active than vancomycin against a range of Gram-positive and Gram-negative bacteria, giving MIC values of 2, 0.125, 1 and 2 µg/ml, respectively, against *Escherichia coli* ESS, several strains of *Staphylococcus aureus*, *Staphylococcus epidermidis* 11047 and *Streptococcus faecalis* I. Other exemplified quinoline derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
279599	OMe	H	vinyl	cyclobutyl		C ₂₅ H ₃₄ N ₂ O
279600	N3	OH	Et	C6H13	3R,4R	C ₂₆ H ₃₉ N ₃ O
279601	4-Pip-CH2O	H	Et	C6H13	3R,4R	C ₃₂ H ₅₁ N ₃ O

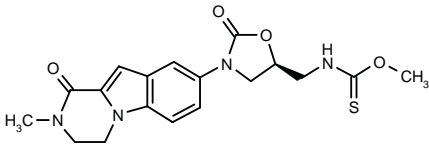
SOURCE – SmithKline Beecham.

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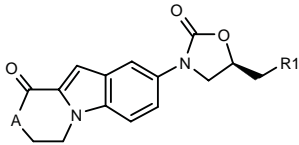
279615

N-[3-(2-Methyl-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]-indol-8-yl)-2-oxooxazolidin-5(*S*)-ylmethyl]thiocarbamic acid *O*-methyl ester



C18 H20 N4 O4 S; Mol wt: 388.4460

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria such as *Staphylococcus aureus* strain 133 (MIC < 0.25 µg/ml), certain Gram-negative bacteria, as well as mycobacteria such as *Mycobacterium smegmatis* DSM 43465 (MIC = 0.25 µg/ml), *Haemophilus influenzae* and anaerobes. Other compounds from this series of tricyclic indolene substituted oxazolidinones include the following:



Compound	R1	A	Formula
279616	NHCO2Me	O	C ₁₇ H ₁₇ N ₃ O ₆
279617	OH	N(Me)	C ₁₈ H ₁₇ N ₃ O ₄
279618	NHAc	N(Me)	C ₁₈ H ₂₀ N ₄ O ₄
279619	NHCOEt	N(Me)	C ₁₉ H ₂₂ N ₄ O ₄
279620	NHCO2Me	N(Me)	C ₁₈ H ₂₀ N ₄ O ₅

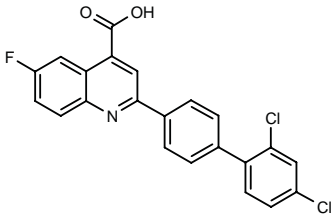
SOURCE – Bayer.

REFERENCES

1. Ruppelt, M. et al. (Bayer AG) *Tricyclic indolene subst. oxazolidinones*. DE 19802235, WO 9937652.

279806

2-(2',4'-Dichlorobiphenyl-4-yl)-6-fluoroquinoline-4-carboxylic acid



C22 H12 Cl2 F N O2; Mol wt: 412.2458

ACTION – Antibacterial agent, an inhibitor of methionyl-tRNA synthetase with good selectivity for enzyme from *Staphylococcus aureus* over human enzyme (IC₅₀ = 1.2 and 31 µM, respectively) and *in vitro* antibacterial activity against *S. aureus* (MIC = 12.5 µg/ml).

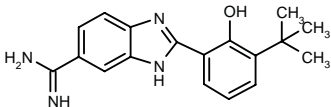
SOURCE – Cubist.

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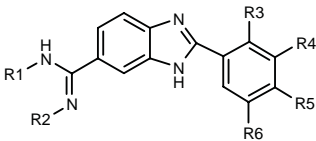
280353¹

2-(3-*tert*-Butyl-2-hydroxyphenyl)-1*H*-benzimidazole-6-carboxamide



C18 H20 N4 O; Mol wt: 308.3830

ACTION – Antibacterial agent that acts by inhibiting the autophosphorylation of bacterial histidine kinases; it demonstrated a broad spectrum of activity against bacterial strains and is reported to be useful as a bacteriostatic and bactericidal agent. Other compounds from this series of 2-substituted phenylbenzimidazoles include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
280354 ¹	H	H	H	OC10H21	OC10H21	H	C ₃₄ H ₅₂ N ₄ O ₂
280355 ^{1,2}	H	H	OH	t-Bu	H	t-Bu	C ₂₂ H ₂₈ N ₄ O
280356 ¹	-(CH2)2-		OH	t-Bu	H	t-Bu	C ₂₄ H ₃₀ N ₄ O

SOURCE – Ortho-McNeil.

REFERENCES

1. Ohemeng, K.A. and Nguyen, V.N. (Ortho Pharmaceutical Corp.) *2-Substd. phenyl-benzimidazole antibacterial agents*. US 5942532.

2. Hilliard, J.J. et al. *Multiple mechanisms of action for inhibitors of histidine protein kinases from bacterial two-component systems*. Antimicrob Agents Chemother 1999, 43(7): 1693.

D2A21^{1-6,9-15}

255574

L-Phenylalanyl-L-alanyl-L-lysyl-L-lysyl-L-phenylalanyl-L-alanyl-L-lysyl-L-lysyl-L-phenylalanyl-L-lysyl-L-lysyl-L-phenylalanyl-L-alanyl-L-lysyl-L-lysyl-L-phenylalanyl-L-alanyl-L-lysyl-L-phenylalanyl-L-alanyl-L-phenylalanyl-L-alanyl-L-phenylalanine

C144 H212 N32 O24; Mol wt: 2775.4590

ACTION – Antibacterial peptide active against clinical isolates of multidrug-resistant cystic fibrosis pathogens including methicillin-resistant *Staphylococcus aureus* (MIC = 0.25-4 µg/ml), multidrug-resistant *Pseudomonas aeruginosa* (MIC = 0.152-4 µg/ml) and multidrug-resistant *Stenotrophomonas maltophilia* (MIC = 0.5-16 µg/ml). The naturally occurring tracheal antimicrobial peptide (TAP) was less active than compound, with MICs ranging from 32 to 64 µg/ml or more. Compound was also reported to be active *in vitro* against several tumor cell lines including cervical, colon, bladder, lung and prostate cancer cells (LD₅₀ = 0.6-1.8 µM), as well as *in vivo* in the Dunning R-3327 rat prostate adenocarcinoma model. Antimicrobial activity of D2A21 against vaginal microorganisms including *Neisseria gonorrhoeae* and *Trichomonas vaginalis* was also described. Compound appeared to interact with the lipid component of the membranes of cancer cells and bacteria, causing lysis and cell death. Another related peptide is:

L-Phenylalanyl-L-lysyl-L-leucyl-L-arginyl-L-alanyl-L-lysyl-L-isoleucyl-L-lysyl-L-valyl-L-arginyl-L-leucyl-L-arginyl-L-alanyl-L-lysyl-L-isoleucyl-L-lysyl-L-leucine

D4E1 [255575]^{2,3,7-9,11,12,14,15}: C98 H181 N31 O18

SOURCE – Demegen.

REFERENCES

1. Enright, F.M. et al. (Demegen, Inc.;Louisiana State University) *Ligand/lytic peptide compsns. and methods of use*. WO 9842364, WO 9842365, WO 9911282.

2. Jaynes, J. (Demegen, Inc.) *Ubiquitin-lytic peptide fusion gene constructs, protein products deriving therefrom, and methods of making and using same*. WO 9603522.

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5. Arlotti, J.A. et al. *Efficacy of a synthetic lytic peptide in the treatment of prostate cancer*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3461.

6. Coleman, M.S. et al. *In vitro activity of an antimicrobial peptide for use as a vaginal microbicide*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct1, Toronto) 1997, Abst F-44.

7. De Lucca, A. et al. *Comparison of synthetic peptide D4E1 and cecropin A on fungal viability*. 96th Gen Meet Am Soc Microbiol (May 19-23, New Orleans) 1996, Abst A-65.

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9. Jaynes, J. et al. *Comparison of the antibacterial activity and toxicity of synthetic membrane interactive peptides (Peptidyl MIMs™)*. 97th Gen Meet Am Soc Microbiol (May 4-8, Miami Beach) 1997, Abst A-110.

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11. Schwab, U. et al. *In vitro activities of designed antimicrobial peptides against multidrug-resistant cystic fibrosis pathogens*. Antimicrob Agents Chemother 1999, 43(6): 1435.

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13. Wu, S.-P. et al. *Peptide D2A21 acts as an antitumor agent in prostate primary cultures*. Proc Amer Assoc Cancer Res 1999, 40: Abst 15.

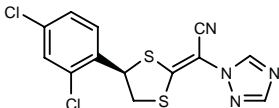
14. *Demegen peptides active against multidrug-resistant bacteria*. DailyDrugNews.com (Daily Essentials) 1999, July 6.

15. *Demegen receives patent protection for Peptidyl MIMs in cancer indications*. DailyDrugNews.com (Daily Essentials) 1998, Oct 14.

ANTIFUNGAL AGENTS

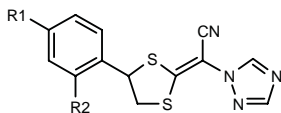
279444

2-[4(R)-(2,4-Dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-(1H-1,2,4-triazol-1-yl)acetonitrile



C13 H8 Cl2 N4 S2; Mol wt: 355.2722

ACTION – Orally active antifungal agent with potent activity against *Aspergillus*, as demonstrated *in vitro* (MIC = 0.008 µg/ml against *Aspergillus fumigatus* TIMM1728) and *in vivo* in a murine model of systemic aspergillosis, mean survival time being 6.4 and 14.0 days, respectively, at 10 and 50 mg/kg/day p.o. x 3 days compared to 3.2 and 7.0 days, respectively, for itraconazole at the same doses. Other compounds from this series of triazole derivatives include the following:



Compound	R1	R2	Isomer	Formula
279445	H	Cl	racemic	C ₁₃ H ₉ ClN ₄ S ₂
279446	H	Cl	R	C ₁₃ H ₉ ClN ₄ S ₂
279447	F	F	racemic	C ₁₃ H ₈ F ₂ N ₄ S ₂
279448	F	F	R	C ₁₃ H ₈ F ₂ N ₄ S ₂
279449	Cl	Cl	racemic	C ₁₃ H ₈ Cl ₂ N ₄ S ₂

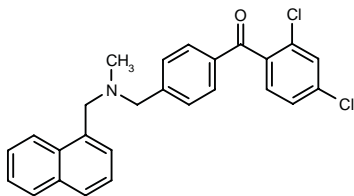
SOURCE – Nihon Nohyaku.

REFERENCES

1. Kagawa, T. et al. (Nihon Nohyaku Co., Ltd.) *Triazole derivs., antimycotic agents, and uses thereof*. WO 9933826.

279676

1-(2,4-Dichlorophenyl)-1-[4-[N-methyl-N-(1-naphthylmethyl)aminomethyl]phenyl]methanone



C26 H21 Cl2 N O; Mol wt: 434.3639

ACTION – Antifungal agent with greater activity than naftifine and clotrimazole against *Sporothrix schenckii* (MIC = 0.31, 20 and 20 mg/l, respectively) and *Epidermophyton floccosum* (MIC = 0.16, 0.63 and 10 mg/l, respectively).

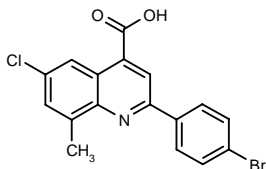
SOURCE – Second Military Medical University, Shanghai (CN).

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279805

2-(4-Bromophenyl)-6-chloro-8-methylquinoline-4-carboxylic acid



C17 H11 Br Cl N O2; Mol wt: 376.6359

ACTION – A potent and selective inhibitor of *Candida albicans* prolyl-tRNA synthetase versus human enzyme (IC₅₀ = 0.005 and > 20 μM, respectively), which, however, is devoid of activity in whole cells (MIC > 100 μg/ml against *C. albicans*).

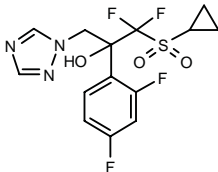
SOURCE – Cubist.

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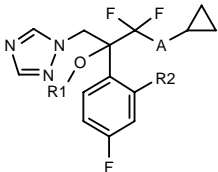
280144

1-(Cyclopropylsulfonyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-1,2,4-triazol-1-yl)-2-propanol



C14 H13 F4 N3 O3 S; Mol wt: 379.3327

ACTION – Oral antifungal agent with potent activity against *Candida albicans* ATCC 44859 (terminal point = 31.3 ng/ml) and *Aspergillus fumigatus* IFM 40808 (MIC = 8 μg/ml), being more potent than fluconazole (terminal point = 250 ng/ml; MIC > 128 μg/ml). *In vivo*, it also significantly increased survival compared to control and fluconazole-treated mice infected with *C. albicans* when given at 1.25 mg/kg/day p.o. x 4 days. Other exemplified compounds from this series of triazole derivatives include the following:



Compound	R1	R2	A	Formula
280145	H	F	S	C ₁₄ H ₁₃ F ₄ N ₃ OS
280146	H	H	S	C ₁₄ H ₁₄ F ₃ N ₃ OS
280147	Me	F	S	C ₁₅ H ₁₅ F ₄ N ₃ OS
280148	Me	F	SO2	C ₁₅ H ₁₅ F ₄ N ₃ O ₃ S
280149	H	F	SO2	C ₁₄ H ₁₃ F ₄ N ₃ O ₃ S

SOURCE – SSP.

REFERENCES

1. Takeda, S. et al. (SSP Co., Ltd.) *Triazole deriv. or salt thereof, preparation process thereof and pharmaceutical containing said cpd. as an effective ingredient (antimycotic)*. CA 2260421, EP 933368, JP 99279160.

TKR-2999

279224

ACTION – Antifungal antibiotic isolated from a culture of fungal strain TKR2999 (FERM BP-6524), proven active against *Candida albicans* TIMM 0136 (MIC = 6.25 μg/ml), *Candida kefir* TIMM 0301 (MIC = 12.5 μg/ml), *Cryptococcus neoformans* TIMM 0354 (MIC = 6.25 μg/ml) and *Aspergillus fumigatus* TIMM 1776 (MIC = 0.78 μg/ml).

SOURCE – Takara Shuzo.

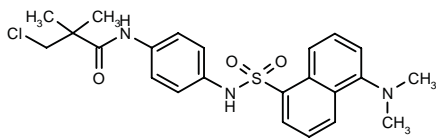
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1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Antibiotic TKR2999, process for the preparation thereof and microbe*. WO 9932498.

ANTIVIRAL DRUGS

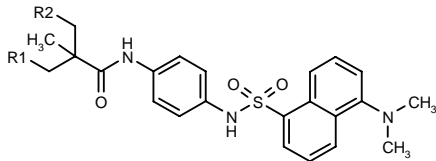
279331

3-Chloro-*N*-[4-[5-(dimethylamino)-1-naphthylsulfon-amido]phenyl]-2,2-dimethylpropionamide



C23 H26 Cl N3 O3 S; Mol wt: 459.9954

ACTION – Antiviral agent for the treatment of cytomegalovirus (CMV) infections with an IC₅₀ value of 0.028 μM against HCMV in infected HELF cells. Within this series of naphthyl-substituted and anilide-substituted sulfonamides, the following are also included:



Compound	R1	R2	Formula
279332	H	H	C ₂₃ H ₂₇ N ₃ O ₃ S
279333	OH	H	C ₂₃ H ₂₇ N ₃ O ₄ S
279334	F	H	C ₂₃ H ₂₆ FN ₃ O ₃ S
279335	OH	OH	C ₂₃ H ₂₇ N ₃ O ₅ S
279336	NH2	H	C ₂₃ H ₂₈ N ₄ O ₃ S

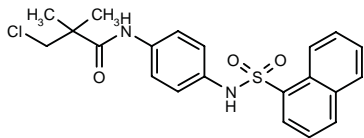
SOURCE – Bayer.

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1. Bender, W. et al. (Bayer AG) *Novel naphthyl-substd. and anilide-substd. sulfonamides*. WO 9937609.

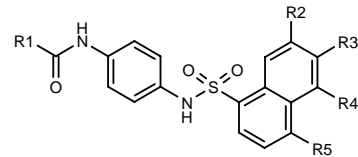
279350

3-Chloro-2,2-dimethyl-*N*-[4-(1-naphthylsulfonamido)-phenyl]propionamide



C21 H21 Cl N2 O3 S; Mol wt: 416.9269

ACTION – Antiviral agent for the treatment of cytomegalovirus (CMV) infections with an IC₅₀ value of 0.087 μM against HCMV in infected HELF cells. Within this series of naphthyl-substituted and heterocyclic-substituted sulfonamides, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
279351	C(Me)2-CH2Cl	H	H	H	Me	C ₂₂ H ₂₃ ClN ₂ O ₃ S
279352	C(Me)2-CH2F	H	H	H	H	C ₂₁ H ₂₁ FN ₂ O ₃ S
279353	t-Bu	OEt	H	H	H	C ₂₃ H ₂₈ N ₂ O ₄ S
279354	C(Me)2-CH2F	H	OCH2Ph	H	H	C ₂₈ H ₂₇ FN ₂ O ₄ S
279355	1-Me-cyclopropyl	H	H	H	H	C ₂₁ H ₂₆ N ₂ O ₃ S
279356	C(Me)2-CH2Cl	H	H	CO2Me	H	C ₂₃ H ₂₃ ClN ₂ O ₅ S
279357	C(Me)2-CH2F	H	H	SO2N-(Me)2	H	C ₂₃ H ₂₆ FN ₃ O ₅ S ₂
281579	t-Bu	H	H	H	H	C ₂₁ H ₂₂ N ₂ O ₃ S
281580	t-Bu	H	H	H	Me	C ₂₂ H ₂₄ N ₂ O ₃ S

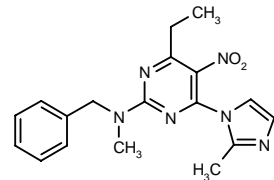
SOURCE – Bayer.

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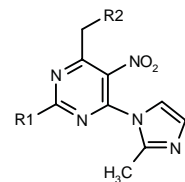
280063

N-Benzyl-*N*-[4-ethyl-6-(2-methyl-1*H*-imidazol-1-yl)-5-nitropyrimidin-2-yl]-*N*-methylamine



C18 H20 N6 O2; Mol wt: 352.3960

ACTION – Antiviral agent for the treatment of human cytomegalovirus (HCMV) infections with an IC₅₀ value of 0.01 μM when tested *in vitro* against HCMV in infected human foreskin fibroblasts (HFF). Other compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	Formula
280064	N(Me)Ph	Me	C ₁₇ H ₁₈ N ₆ O ₂
280065	N(Me)CH2Ph	H	C ₁₇ H ₁₈ N ₆ O ₂
280066	4-PhCH2-1-Piz	H	C ₂₀ H ₂₃ N ₇ O ₂

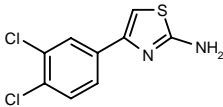
SOURCE – Tularik.

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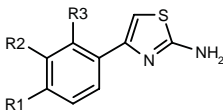
280264

4-(3,4-Dichlorophenyl)thiazol-2-amine



C9 H6 Cl2 N2 S; Mol wt: 245.1324

ACTION – Antiviral agent particularly useful for the treatment or prevention of herpes simplex virus (HSV) infections, with demonstrated antiviral activity in an HSV-1 gel primase assay (IC₅₀ = 5 μM). It is believed to exert its antiviral activity by interfering with the herpes helicase-primase enzyme, thereby inhibiting herpesvirus DNA replication. As this enzyme is conserved across human herpesviruses, the compound is also expected to be useful in other herpesvirus infections, including varicella-zoster virus and cytomegalovirus infections. Other representative compounds from this series of heteroaryl-substituted benzenes are:



Compound	R1	R2	R3	Formula
280265	NO2	H	H	C ₉ H ₇ N ₃ O ₂ S
280266	Cl	NO2	H	C ₉ H ₆ ClN ₃ O ₂ S
280267	H	H	I	C ₉ H ₇ IN ₂ S

SOURCE – Tularik.

REFERENCES

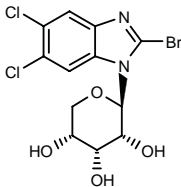
1. Flygare, J.A. et al. (Tularik Inc.) *Antiviral agents.* WO 9942455.

GR-275175X

258533

2-Bromo-5,6-dichloro-1-β-D-ribosepyranosyl-1H-benzimidazole

GW-275175
GW-275175X



C12 H11 Br Cl2 N2 O4; Mol wt: 398.0389

ACTION – Antiviral agent with potent *in vitro* activity against human cytomegalovirus (HCMV; IC₅₀ = 0.70, 1.4 and 0.40 μM, respectively, in DNA hybridization, plaque reduction and yield reduction assays) and potency comparable to that of ganciclovir (IC₅₀ = 0.53, 7.2 and 0.4 μM, respectively). It showed a favorable oral pharmacokinetic profile and was selected as a follow-up compound to 1263W94 for the treatment of HCMV infections.

SOURCE – Glaxo Wellcome.

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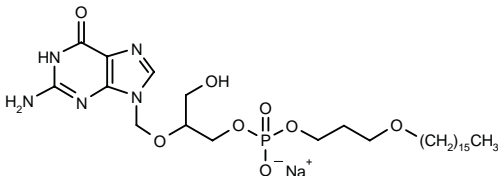
2. Boyd, F.L. et al. *Synthesis and evaluation of a series of 1H-benzimidazole pyranosides as anti-human cytomegalovirus agents.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 283.

3. *Glaxo Wellcome's R&D pipeline remains full and diverse.* DailyDrugNews.com (Daily Essentials) 1998, Jan 21.

HDP-GCV

251059

9-[2-[3-(Hexadecyloxy)propoxy(hydroxy)phophoryloxy]-1-(hydroxymethyl)ethoxymethyl]guanine sodium salt



C28 H51 N5 Na O8 P; Mol wt: 639.7019

ACTION – Antiviral agent, a lipid prodrug of ganciclovir with 2.5-fold improved *in vitro* activity against human cytomegalovirus (HCMV; IC₅₀ = 0.64 μM) and equivalent activity against herpes simplex virus type 1 in human lung fibroblasts (HSV-1; IC₅₀ = 0.023 μM). *In vivo* in HSV-1-infected mice, compound (1.28-25 mg/kg p.o.) exhibited strong antiviral activity similar to that of ganciclovir. When administered intravitreally in selfassembling liposomes, it exhibited potent and long-lasting efficacy compared to ganciclovir in HSV-1 retinitis after a single administration.

SOURCE – University of California, San Diego, San Diego, CA (US).

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2. Gardner, M.F. et al. *Intravitreal toxicology and treatment efficacy of a long acting anti-viral lipid prodrug ganciclovir (HDP-GCV).* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4593.

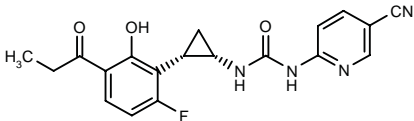
3. Rybak, R.J. et al. *Oral activity of 1-O-hexadecyl-propanediol-3-phospho-acyclovir (HDP-ACV) and HDP-P ganciclovir (HDP-GCV) in herpes simplex virus (HSV) and murine cytomegalovirus (MCMV) infections of mice.* Antivir Res 1999, 41(2): Abst 127.

4. Strah, S. et al. *Effect of alkoxy chain length on the vitro antiviral activity of ganciclovir monophosphate alkoxypropyl esters.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 288.

AIDS MEDICINES

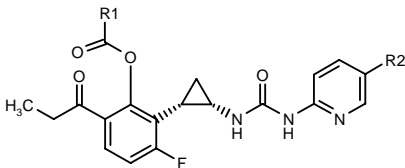
278983

N-(5-Cyanopyridin-2-yl)-N'-[(1*S*,2*S*)-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]urea



C19 H17 F N4 O3; Mol wt: 368.3663

ACTION – Antiviral agent for AIDS, a non-nucleoside HIV reverse transcriptase inhibitor with an improved resistance pattern and pharmacokinetic profile and a prolonged time to development of virus resistance as compared to structurally related compounds. *In vitro*, it exhibited high antiviral activity in MT-4 cells infected with both wild-type and mutant strains of HIV such as K103N and Y181C (IC₅₀ = 0.0007, 0.037 and 0.006 µg/ml, respectively). Other specifically claimed compounds from this series of thiourea derivatives include the following:



Compound	R1	R2	Formula
278984	6-(MeNH)-3-Pyr	CN	C ₂₆ H ₂₃ FN ₆ O ₄
278985	3-NH2-Ph	Br	C ₂₅ H ₂₂ BrFN ₄ O ₄

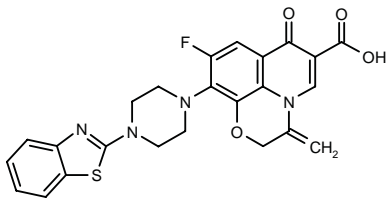
SOURCE – Medivir.

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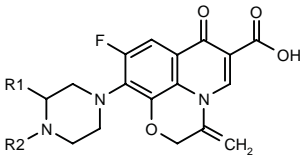
279450

10-[4-(2-Benzothiazolyl)-1-piperazinyl]-9-fluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid



C24 H19 F N4 O4 S; Mol wt: 478.5021

ACTION – Antiviral agent with potent activity against HIV in infected MT-4 cells (IC₅₀ = 0.008 µg/ml), as well as against HCMV in infected human fetal fibroblast MRC-5 cells (IC₅₀ = 0.016 µg/ml), and reduced cytotoxic potential in uninfected MT-4 cells (CC₅₀ = 0.16 µg/ml). Other compounds from this series of fused quinolinecarboxylic acid derivatives include the following:



Compound	R1	R2	Formula
279451	H	6-MeO-2-benzothiazolyl	C ₂₅ H ₂₁ FN ₄ O ₅ S
279452	H	2-Pyr	C ₂₂ H ₁₉ FN ₄ O ₄
279453	H	Ph	C ₂₃ H ₂₀ FN ₃ O ₄
279454	H	4-MeO-Ph	C ₂₄ H ₂₂ FN ₃ O ₅
279455	Me	2-pyrimidinyl	C ₂₂ H ₂₀ FN ₅ O ₄

SOURCES – Sankyo; Ube.

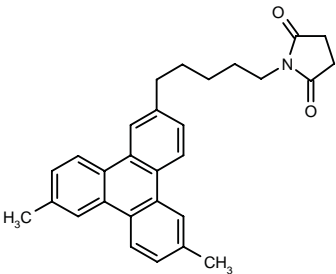
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TDS1

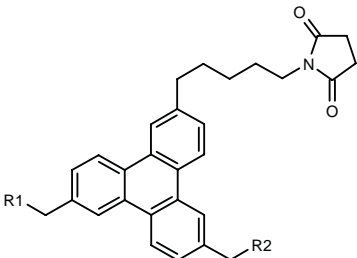
280287

1-[5-(6,10-Dimethyl-2-triphenylenyl)pentyl]pyrrolidine-2,5-dione



C29 H29 N O2; Mol wt: 423.5531

ACTION – Anti-HIV agent which acts as an allosteric inhibitor of Tat protein; it inhibits HIV-1 transactivation by acting directly on Tat, as well as the Tat-TAR interaction. TDS1 exerted anti-HIV-1 activity in MT-4 cells and exhibited low cytotoxicity in human cell lines and little or no toxicity in rats and mice. Other exemplified functionalized aromatic compounds are:



Compound	R1=R2	Formula
TDS2 [280288]	3(R),5(S)-(OH)2-1-Pip	C ₃₉ H ₄₇ N ₃ O ₆
TDS3 [280289]	3(R),5(S)-(OH)2-cyclohexyl	C ₄₁ H ₄₉ NO ₆
TDS4 [280290]	OH	C ₂₉ H ₂₉ NO ₄

SOURCE – CNRS.

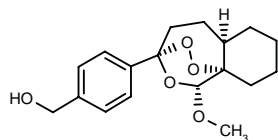
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TREATMENT OF PROTOZOAL DISEASES

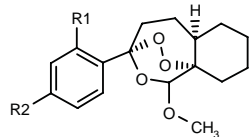
280212

(3*S*,5*aR*,9*aS*,10*R*)-3-(4-Hydroxyphenyl)-10-methoxy-perhydro-3,9*a*-(epoxymethano)-1,2-benzodioxepin



C18 H24 O5; Mol wt: 320.3826

ACTION – Antiparasitic agent particularly useful for the treatment of malaria and cerebral toxoplasmic encephalitis. Antimalarial activity was demonstrated by inhibition of the incorporation of tritiated hypoxanthine by *Plasmodium falciparum* in human red blood cells (IC₅₀ = 15 nM). Other compounds from this series of 3-substituted trioxanes include the following:



Compound	R1	R2	Isomer	Formula
280213	H	Ph	10(S)	C ₂₃ H ₂₆ O ₄
280214	H	F	10(S)	C ₁₇ H ₂₁ FO ₄
280215	Me	F	10(R)	C ₁₈ H ₂₃ FO ₄
280216	Me	F	10(S)	C ₁₈ H ₂₃ FO ₄
280217	H	H	10(S)	C ₁₇ H ₂₂ O ₄

SOURCE – Johns Hopkins University, Baltimore, MD (US).

REFERENCES

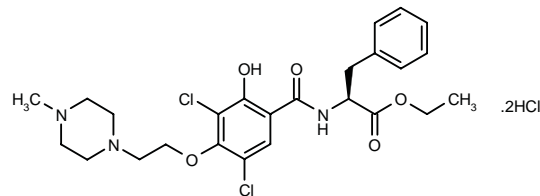
1. Posner, G.H. et al. (Johns Hopkins University) *C3 substd. trioxanes useful as antiparasitic drugs.* US 5932591.

TREATMENT OF SEPTIC SHOCK

JTE-607

280305

N-[3,5-Dichloro-2-hydroxy-4-[2-(4-methyl-1-piperazinyl)-ethoxy]benzoyl]-*L*-phenylalanine ethyl ester dihydrochloride



C25 H31 Cl2 N3 O5 . 2HCl; Mol wt: 597.3637

ACTION – Antiinflammatory agent, an inhibitor of the production of inflammatory cytokines including TNF- α , IL-1 β , IL-6, IL-8 and IL-10, as demonstrated in lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 11, 5.9, 8.8, 7.3 and 9.1 nM, respectively), being much more potent than prednisolone and specific for human monocytes. Compound also inhibited other cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-1 receptor antagonist (IL-1RA), with IC₅₀ values of 2.4 and 5.4 nM, respectively. In a murine model of endotoxemia after burn injury, where the administration of LPS induced an increase in the production of TNF- α and macrophage inflammatory protein 2 α (MIP-2 α), compound (10-100 mg/kg/day s.c. for 10 days) dose-dependently attenuated production of the cytokines and improved survival rate. In another model of endotoxemia caused by LPS administration to *Corynebacterium parvum*-sensitized mice, compound (3-10 mg/kg i.v.) significantly reduced mortality and TNF- α plasma levels. Potentially useful for the treatment of various cytokine-mediated diseases including septic shock, without causing immunosuppression.

SOURCE – Japan Tobacco.

REFERENCES

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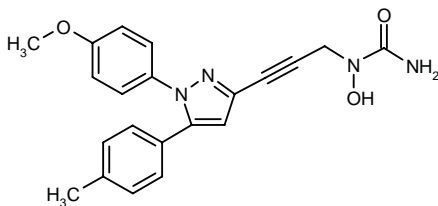
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

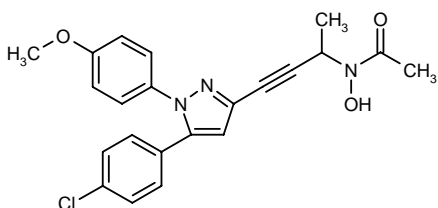
275256

N-Hydroxy-*N*-[3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-1*H*-pyrazol-3-yl]-2-propynyl]urea



C21 H20 N4 O3; Mol wt: 376.4140

ACTION – 5-Lipoxygenase (5-LO) inhibitor (IC_{50} = 0.07 and 4.7 μ M in broken and intact RBL-1 cells, respectively) with additional cyclooxygenase (COX)-inhibitory activity, as demonstrated in sheep seminal vesicles where the constitutive isoform COX-1 is predominant (IC_{50} = 1.02 μ M) and in broken (IC_{50} = 0.31 μ M) and intact RBL-1 cells (IC_{50} = 12.1 μ g/ml). In an *ex vivo* assay in canine blood, compound (5 mg/kg p.o.) was able to inhibit both COX and 5-LO enzymes (82 and 53% inhibition, respectively, at 2 h), but with a shorter duration of 5-LO-inhibitory activity than the reference compound tepoxalin. Another representative compound within this series of hybrid molecules derived from tepoxalin and ABT-761 is:



275258: C22 H20 Cl N3 O3

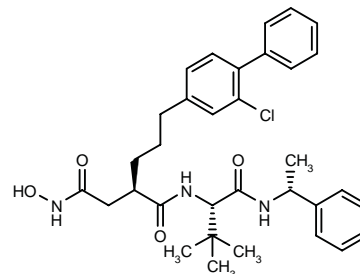
SOURCE – R.W. Johnson.

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- Connolly, P. et al. (Ortho Pharmaceutical Corp.) *Acetylenic 1,5-diarylpyrazoles as antiinflammatory agents*. US 5925769.
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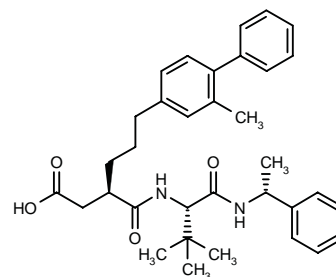
278853

2(*R*)-[3-(2-Chlorobiphenyl-4-yl)propyl]-*N*¹-[2,2-dimethyl-1(*S*)-[*N*-[1(*R*)-phenylethyl]carbamoyl]propyl]-*N*⁴-hydroxysuccinamide



C33 H40 Cl N3 O4; Mol wt: 578.1490

ACTION – Potent inhibitor of the matrix metalloproteinase MMP-3 (stromelysin 1; IC_{50} = 13.5 nM) with 94-fold selectivity relative to MMP-2 (gelatinase A; IC_{50} = 1269 nM); it is also active against MMP-13 (collagenase 3; IC_{50} = 130 nM). Potentially useful for the treatment of arthritis, ulcerative colitis, duodenal ulcers, skin disorders and cardiac and cerebral infarction. Another exemplified compound is:



278854: C34 H42 N2 O4

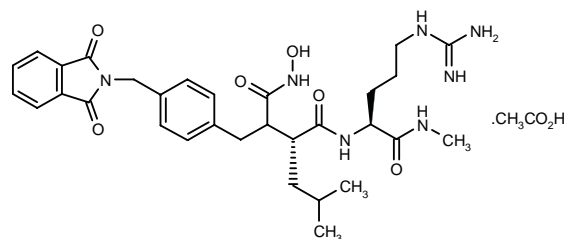
SOURCE – Pfizer.

REFERENCES

- Fray, M.J. et al. (Pfizer Ltd.;Pfizer Inc.) *Matrix metalloprotease inhibitors*. WO 9935124.

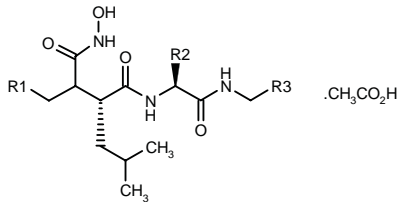
279122

*N*²-[4-(Hydroxyamino)-2(*R*)-isobutyl-3-[4-(phthalimido-methyl)benzyl]succinyl]-*N*¹-methyl-L-argininamide acetate

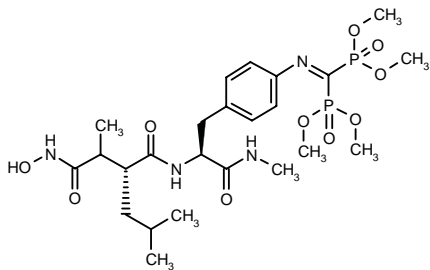


C31 H41 N7 O6 . C2 H4 O2; Mol wt: 667.7595

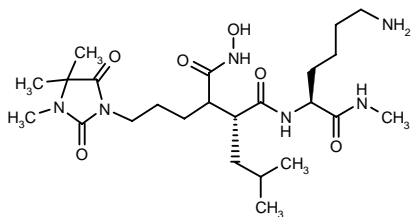
ACTION – Matrix metalloproteinase (MMP) inhibitor with potent activity against human fibroblast collagenase (MMP-1; IC₅₀ = 9 nM) and human stromelysin 1 (MMP-3; IC₅₀ = 2 nM), also shown to inhibit TNF-α convertase (TACE) in lipopolysaccharide-stimulated human monocytic leukemia U937 cells (IC₅₀ = 426 nM). Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
279127	CH2CH2Ph	(CH2)4N-C(=NH)Me	CH2OH	C ₂₇ H ₄₄ N ₄ O ₅ .C ₂ H ₄ O ₂
279128	4-(4-Me-PhSO2-NHCH2)-Ph	(CH2)3NH-C(=NH)NH2	H	C ₃₀ H ₄₅ N ₇ O ₆ S .C ₂ H ₄ O ₂
279129	4-(NH2CH2)-PhCH2CH2	t-Bu	H	C ₂₅ H ₄₂ N ₄ O ₄ .C ₂ H ₄ O ₂
279130	4-(NH2CH2)-PhCH2CH2	(CH2)3NH2	H	C ₂₄ H ₄₁ N ₅ O ₄ .C ₂ H ₄ O ₂



279126: C24 H40 N4 O10 P2



279131: C24 H44 N6 O6

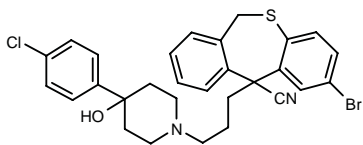
SOURCE – Fuji Yakuhin.

REFERENCES

1. Fujisawa, T. et al. (Fuji Yakuhin Kogyo Co., Ltd.) *Novel metalloproteinase inhibitors*. WO 9931052.

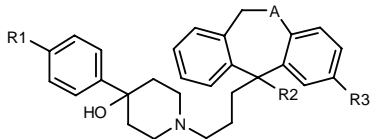
279303

2-Bromo-11-[3-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]propyl]-6,11-dihydrodibenzo[b,e]thiepine-11-carbonitrile



C29 H28 Br Cl N2 O S; Mol wt: 567.9762

ACTION – Chemokine CCR1 receptor antagonist (IC₅₀ < 1 μM against [¹²⁵I]-RANTES and [¹²⁵I]-MIP-1α binding in THP-1 cell membranes) with potential in the treatment of diseases associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines such as chronic inflammatory disorders, atherosclerosis, ischemia–reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel disease, transplant rejection, graft-versus-host disease, allergies and asthma. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
279304	F	CN	H	O	C ₂₉ H ₂₉ FN ₂ O ₂
279305	Cl	CN	Br	O	C ₂₉ H ₂₈ BrClN ₂ O ₂
279306	Cl	H	H	O	C ₂₈ H ₃₀ ClNO ₂
279307	F	CN	H	S	C ₂₉ H ₂₉ FN ₂ OS

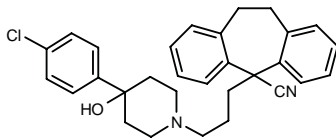
SOURCES – Kyowa Hakko; LeukoSite.

REFERENCES

1. Luly, J.R. et al. (LeukoSite, Inc.;Kyowa Hakko Kogyo Co., Ltd.) *Chemokine receptor antagonists and methods of use therefor*. WO 9937619.

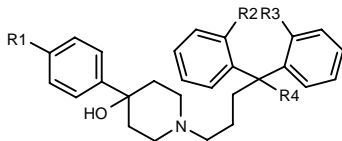
279308

5-[3-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]propyl]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile



C30 H31 Cl N2 O; Mol wt: 471.0409

ACTION – Chemokine receptor antagonist with an IC₅₀ value of 0.052 μM in a binding assay using [¹²⁵I]-RANTES or [¹²⁵I]-MIP-1α as the radioligand in THP-1 cell membranes. Potentially useful in the treatment of diseases associated with aberrant leukocyte recruitment and/or activation, or disorders mediated by chemokines such as arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, AIDS-associated disorders, transplant rejection, graft-versus-host disease, allergies and asthma. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
279309	Cl	-CH=CH-		CN	C ₃₀ H ₂₉ ClN ₂ O
279310	Cl	-CH2S-		CN	C ₂₉ H ₂₉ ClN ₂ OS
279311	Br	-CH2S-		CN	C ₂₉ H ₂₉ BrN ₂ OS
279312	Cl	-CH2SO2-		CN	C ₂₉ H ₂₉ ClN ₂ O ₃ S
279313	Cl	-CH2S-		H	C ₂₈ H ₃₀ ClNOS
279314	Cl	-(CH2)2-		H	C ₂₉ H ₃₂ ClNO

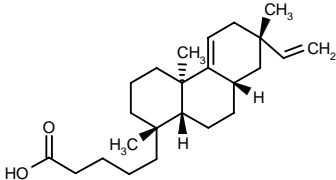
SOURCE – LeukoSite.

REFERENCES

1. Schwender, C.F. et al. (LeukoSite, Inc.) *Chemokine receptor antagonists and methods of use therefor*. WO 9937617.

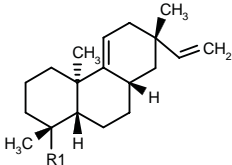
279368

5-[(1*R*,4*aR*,7*R*,8*aS*,10*aR*)-1,4*a*,7-Trimethyl-7-vinyl-1,2,3,4,4*a*,6,7,8,8*a*,9,10,10*a*-dodecahydro-1-phenanthrenyl]pentanoic acid



C24 H38 O2; Mol wt: 358.5622

ACTION- Antiinflammatory and analgesic agent, a semisynthetic derivative of (–)-primara-9(11),15-diene-4-carboxylic acid with cyclooxygenase type 2 (COX-2)-inhibitory activity (IC₅₀ = 38.7 μM against enzyme from sheep placenta vs. 790.4 and 82.0 μM for the parent compound and indomethacin, respectively). Other compounds from this series of diterpene derivatives include the following:



Compound	R1	Formula
279369	CH2CO2H	C ₂₁ H ₃₂ O ₂
279370	CH=CHCO2H	C ₂₂ H ₃₂ O ₂
279371	CONHNH2	C ₂₀ H ₃₂ N ₂ O
279372	CH2CH=CHCO2H	C ₂₃ H ₃₄ O ₂
279373	CH=CHCH=CHCO2H	C ₂₄ H ₃₄ O ₂
279374	4-I-PhSO2NHCOCH=CHCH=CH	C ₃₀ H ₃₈ INO ₃ S

SOURCE – Sae Han Pharmaceuticals.

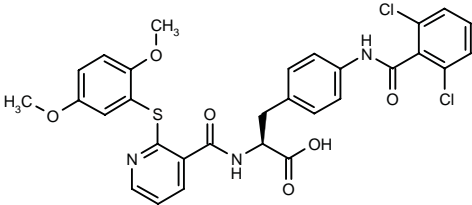
REFERENCES

1. Choi, Y.H. et al. (Sae Han Pharmaceuticals Co., Ltd.) *Diterpene derivs. and anti-inflammatory analgesic agents comprising the same*. WO 9937600.

279462

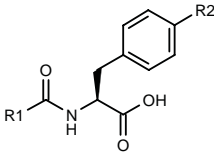
3-[4-(2,6-Dichlorobenzamido)]phenyl]-2 (S)-[2-(2,5-dimethoxyphenylsulfanyl)-3-pyridinylcarboxamido]-propionic acid

4-(2,6-Dichlorobenzamido)-*N*-[2-(2,5-dimethoxyphenylsulfanyl)pyridin-3-ylcarbonyl]-L-phenylalanine



C30 H25 Cl2 N3 O6 S; Mol wt: 626.5145

ACTION – Agent for the treatment of immune or inflammatory disorders, a potent and selective inhibitor of α₄ integrins, particularly α₄β₁ integrin. Other specifically claimed compounds from this series of phenylalanine derivatives include the following:



Compound	R1	R2	Formula
279463	3,5-(Cl)2-4-Pyr	3,5-(Cl)2-4-Pyr-CONH	C ₂₁ H ₁₄ Cl ₄ N ₄ O ₄
279464	2-Cl-3-Pyr	3,5-(Cl)2-4-Pyr-CONH	C ₂₁ H ₁₅ Cl ₃ N ₄ O ₄
279465	4-Ac-1,2,5-(Me)3-3-pyrrolyl	2,6-(Cl)2-PhCH2O	C ₂₈ H ₂₆ Cl ₂ N ₂ O ₅
279466	3-(3-Pyr-CH2S)-4-Pyr	3,5-(Cl)2-4-Pyr-CONH	C ₂₇ H ₂₁ Cl ₂ N ₅ O ₄ S
279467	4-Ac-1,2,5-(Me)3-3-pyrrolyl	3,5-(Cl)2-4-Pyr-CONH	C ₂₅ H ₂₄ Cl ₂ N ₄ O ₅

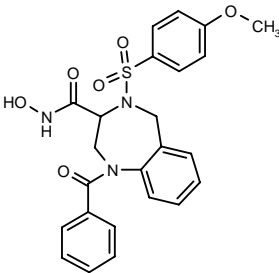
SOURCE – Celltech (Celltech Chiroscience).

REFERENCES

1. Head, J.C. et al. (Celltech Therapeutics Ltd.) *Phenylalanine derivs. useful as pharmaceutical agents*. WO 9937618.

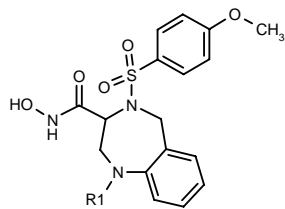
279602

1-Benzoyl-4-(4-methoxyphenylsulfonyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-3-carboxylic acid



C24 H23 N3 O6 S; Mol wt: 481.5267

ACTION – Matrix metalloproteinase (MMP) inhibitor with particularly potent activity against MMP-9 (gelatinase B) and MMP-13 (collagenase 3), as well as MMP-1 (fibroblast collagenase) and TACE (TNF- α -converting enzyme). Potentially useful in the treatment of MMP-mediated disease conditions such as osteoarthritis, rheumatoid arthritis, degenerative cartilage loss and tumor growth. Other exemplified 2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine-3-hydroxamic acids are:



Compound	R1	Formula
279603	4-Me-PhSO2	C ₂₄ H ₂₈ N ₃ O ₇ S ₂
279604	SO2Pr	C ₂₀ H ₂₈ N ₃ O ₇ S ₂
279605	3-Pyr-CO	C ₂₃ H ₂₂ N ₄ O ₆ S
279606	2-thienyl-CO	C ₂₂ H ₂₁ N ₃ O ₆ S ₂
279607	COCH2OMe	C ₂₀ H ₂₃ N ₃ O ₇ S
279608	cyclopropyl-CO	C ₂₁ H ₂₃ N ₃ O ₆ S
279609	2-furyl-CO	C ₂₂ H ₂₁ N ₃ O ₇ S

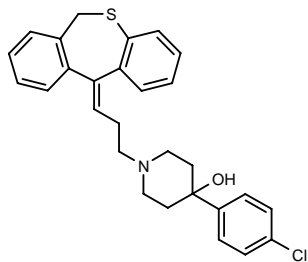
SOURCE – American Home Products.

REFERENCES

1. Albright, J.D. et al. (American Cyanamid Co.) 2,3,4,5-Tetrahydro-1*H*-[1,4]-benzodiazepine-3-hydroxamic acids as matrix metalloproteinase inhibitors. WO 9937625.

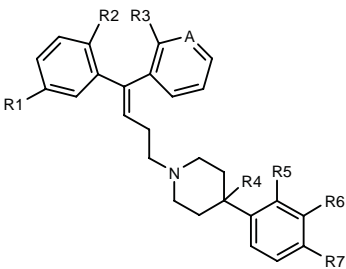
279627

4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenzo[*b,e*]thiepin-11-ylidene)propyl]piperidin-4-ol



C28 H28 Cl N O S; Mol wt: 462.0542

ACTION – Chemokine receptor antagonist with an IC₅₀ < 1 μ M for inhibition of specific binding of [¹²⁵I]-RANTES or [¹²⁵I]-MIP-1 α in THP-1 cell membranes. Potentially useful in the treatment of diseases associated with aberrant leukocyte recruitment and/or activation or disorders mediated by chemokines such as arthritis, atherosclerosis, ischemia–reperfusion injury, diabetes mellitus, psoriasis, multiple sclerosis, inflammatory bowel disease, transplant rejection, graft-versus-host disease, AIDS-related disorders, allergies and asthma. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	A	Formula
279628	H	-CH=CH-		OH	H	H	Cl	CH	C ₂₉ H ₂₈ ClNO
279629	OEt	-OCH2-		OH	H	H	Cl	CH	C ₃₀ H ₃₂ ClNO ₃
279630	OEt	-OCH2-		OH	H	H	Cl	N	C ₂₉ H ₃₁ ClN ₂ O ₃
279631	H	-CONH-		OH	H	H	Cl	N	C ₂₇ H ₂₆ ClN ₃ O ₂
279632	OMe	-OCH2-		H	H	H	H	N	C ₂₈ H ₃₀ N ₂ O ₂
279633	OMe	-OCH2-		OH	H	Cl	Cl	N	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₃
279634	OMe	-OCH2-		-OCH2-	H	Cl	N		C ₂₉ H ₂₉ ClN ₂ O ₃
279635	OPr	-OCH2-		OH	H	H	Cl	N	C ₃₀ H ₃₃ ClN ₂ O ₃
279636	OCH2-CO2H	-OCH2-		H	H	H	Cl	N	C ₂₉ H ₂₉ ClN ₂ O ₄
279637	OCH(Me)-CO2H	-OCH2-		OH	H	H	Cl	N	C ₃₀ H ₃₁ ClN ₂ O ₅
279638	OMe	-OCH2-		N3	H	H	Cl	N	C ₂₈ H ₂₈ ClN ₃ O ₂

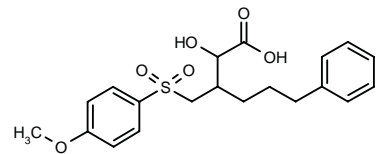
SOURCES – Kyowa Hakko; LeukoSite.

REFERENCES

1. Luly, J.R. et al. (LeukoSite, Inc.;Kyowa Hakko Kogyo Co., Ltd.) Chemokine receptor antagonists and methods of use therefor. WO 9937651.

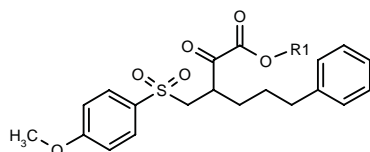
279663

2-Hydroxy-3-(4-methoxyphenylsulfonylmethyl)-6-phenylhexanoic acid

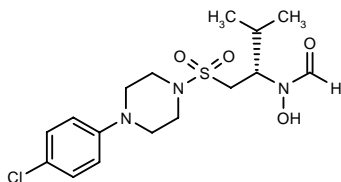


C20 H24 O6 S; Mol wt: 392.4696

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysin, gelatinase and collagenase, as well as of the production of TNF- α , with potential in the treatment of a broad range of disorders including cancer, arthritis, osteoporosis, adult respiratory distress syndrome, Alzheimer’s disease, multiple sclerosis, ulcerative colitis, fever, cardiovascular disorders, cachexia, acute infection, HIV infection, shock states, graft-versus-host reaction, autoimmune disorders and reperfusion injury. Other specifically claimed compounds from this series of hydroxamic and carboxylic acid derivatives include the following:



Compound	R1	Formula
279664	Me	C ₂₁ H ₂₄ O ₆ S
279665	H	C ₂₀ H ₂₂ O ₆ S



279666: C₁₆ H₂₄ Cl N₃ O₄ S

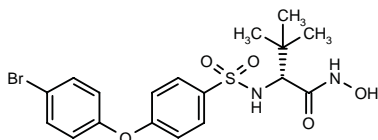
SOURCE – Darwin Discovery.

REFERENCES

1. Montana, J.G. et al. (Darwin Discovery Ltd.) *Hydroxamic and carboxylic acid derivs.* WO 9938843.

279802

*N*²-[4-(4-Bromophenoxy)phenylsulfonyl]-*N*¹-hydroxy-D-*tert*-leucinamide



C₁₈ H₂₁ Br N₂ O₅ S; Mol wt: 457.3429

ACTION – Matrix metalloproteinase inhibitor from a series of sulfonamide acids and hydroxamates derived from D-amino acids.

SOURCE – Agouron.

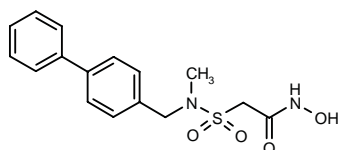
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1. Bender, S.L. and Abreo, M.A. (Agouron Pharmaceuticals, Inc.) *Metalloproteinase inhibitors, pharmaceutical compsns. containing them and their pharmaceutical uses.* WO 9843963.

2. Abreo, M.A. et al. *Sulfonamide acids and hydroxamates derived from D-amino acids are MMP inhibitors.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 77.

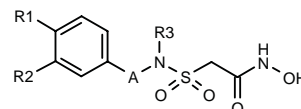
280117

2-[*N*-(4-Biphenyl)methyl]-*N*-methylsulfamoyl]acetohydroxamic acid



C₁₆ H₁₈ N₂ O₄ S; Mol wt: 334.3942

ACTION – An inhibitor of matrix metalloproteinases with selectivity for MMP-3 (stromelysin 1; IC₅₀ = 1.5 μM or less), MMP-13 (collagenase 3) and MMP-2 (gelatinase A; IC₅₀ = 6.3 μM or less). Potentially useful for treating or preventing atherosclerosis, myocardial infarction, heart failure, restenosis, stroke, tissue ulceration, skin disorders, cancer metastasis, tumor angiogenesis, age-related macular degeneration, fibrotic diseases, rheumatoid arthritis, osteoarthritis, as well as for wound repair. Other exemplified compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	A	Formula
280118	Ph	H	H	-(CH ₂) ₂ -	C ₁₆ H ₁₈ N ₂ O ₄ S
280119	Ph	H	H	-OCH ₂ CH ₂ -	C ₁₆ H ₁₈ N ₂ O ₅ S
280120	H	H	Me	-(CH ₂) ₂ -	C ₁₁ H ₁₆ N ₂ O ₄ S
280121	Ph	H	Me	-OCH ₂ CH ₂ -	C ₁₇ H ₂₀ N ₂ O ₅ S
280122	Ph	H	Me	-(CH ₂) ₂ -	C ₁₇ H ₂₀ N ₂ O ₄ S
280123	OPh	H	Me	-CH ₂ -	C ₁₆ H ₁₈ N ₂ O ₅ S
280124	4-CN-Ph	H	Me	-CH ₂ -	C ₁₇ H ₁₇ N ₃ O ₄ S
280126	4-Cl-Ph	H	Me	-CH ₂ -	C ₁₆ H ₁₇ ClN ₂ O ₄ S
280127	Ph	H	Me	-CH=CHCH ₂ -	C ₁₈ H ₂₀ N ₂ O ₄ S
280128	Ph	H	Me	-(CH ₂) ₃ -	C ₁₈ H ₂₂ N ₂ O ₄ S
280129	Ph	Me	Me	-CH=CHCH ₂ -	C ₁₉ H ₂₂ N ₂ O ₄ S

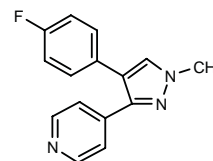
SOURCE – Pfizer.

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1. Dack, K.N. and Whitlock, G.A. (Pfizer Ltd.;Pfizer Inc.) *Metalloprotease inhibitors.* CA 2260337, EP 931788.

280204

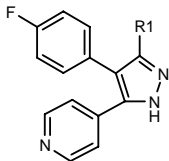
4-[4-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]pyridine



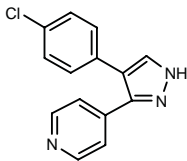
C₁₅ H₁₂ F N₃; Mol wt: 253.2788

ACTION – An inhibitor of p38 MAP (mitogen-activated protein) kinase, particularly p38-α kinase, as demonstrated *in vitro* in the PHAS-I (phosphorylated heat- and acid-stable protein-insulin inducible) and epidermal growth factor receptor peptide phosphorylation assays (IC₅₀ = 7.23 and 0.4 μM, respectively). In addition, it inhibited the production of TNF-α in lipopolysaccharide (LPS)-stimulated human histiocytic lymphoma U937 cells (IC₅₀ = 1.59 μM) and *ex vivo* in LPS-treated mice (76% inhibition at 30 mg/kg p.o. 6 h prior to LPS injection). Potentially useful for the treatment or prevention of a broad range of p38-mediated disorders such as rheumatoid arthritis, osteoarthritis, adult respiratory distress syndrome, asthma, osteoporosis, atherosclerosis, congestive heart failure, cardiac and renal

reperfusion injury, thrombotic disorders, nephritis, graft-versus-host reaction, psoriasis, inflammatory bowel disease, bacterial and viral infections, septic shock and cachexia. A representative compound from a series of 3(5)-heteroaryl substituted pyrazole derivatives, wherein the following are also included:



Compound	R1	Formula
280205	NHSO2NHMe	C ₁₅ H ₁₄ FN ₅ O ₂ S
280206	H	C ₁₄ H ₁₀ FN ₃



280207: C14 H10 Cl N3

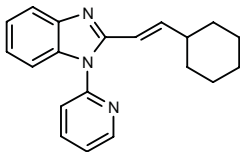
SOURCE – Searle.

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1. Anantanarayan, A. et al. (G.D. Searle & Co.) 3(5)-Heteroaryl subst. pyrazoles as p38 kinase inhibitors. US 5932576.

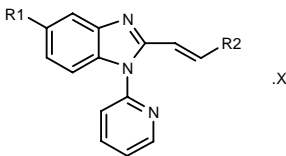
280257

2-[2(E)-Cyclohexylvinyl]-1-(2-pyridyl)-1H-benzimidazole



C20 H21 N3; Mol wt: 303.4069

ACTION – Analgesic and antiinflammatory agent that acts as an inhibitor of cyclooxygenase type 2 (COX-2) and can be administered via the oral, parenteral or topical route. Other specifically claimed benzimidazole derivatives include the following:



Compound	R1	R2	X	Formula
280258	F	Ph		C ₂₀ H ₁₄ FN ₃
280259	OMe	Ph	oxalate	C ₂₁ H ₁₇ N ₃ O.C ₂ H ₂ O ₄
280260	Me	2-thienyl	oxalate	C ₁₉ H ₁₅ N ₃ S.C ₂ H ₂ O ₄
280261	F	cyclohexyl		C ₂₀ H ₂₀ FN ₃
280262	OMe	2-Me-3-furyl		C ₂₀ H ₁₇ N ₃ O ₂

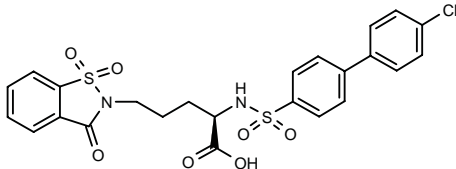
SOURCE – Pfizer.

REFERENCES

1. Okumura, Y. et al. (Pfizer Inc.) Benzimidazole derivs. as cyclooxygenase-2 inhibitors. CA 2261426, EP 937722, JP 99263788.

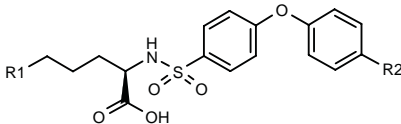
280317

2(R)-(4'-Chlorobiphenyl-4-ylsulfonamido)-5-(1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl)pentanoic acid



C24 H21 Cl N2 O7 S2; Mol wt: 549.0219

ACTION – Matrix metalloproteinase (MMP) inhibitor that inhibits MMPs such as gelatinase, stromelysin, collagenase, macrophage metalloelastase and membrane-type MMPs, and is particularly effective against collagenase 3. Potentially useful particularly for the treatment of inflammatory conditions, rheumatoid arthritis, osteoarthritis and tumors. Other specifically claimed sulfonylamino derivatives are:



Compound	R1	R2	Formula
280318	1-(Me)-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	H	C ₂₆ H ₂₅ N ₃ O ₇ S
280319	1-(Me)-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	F	C ₂₆ H ₂₄ FN ₃ O ₇ S
280320	1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl	F	C ₂₄ H ₂₁ FN ₂ O ₈ S ₂
280321	1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-yl	H	C ₂₄ H ₂₂ N ₂ O ₈ S ₂

SOURCE – Novartis.

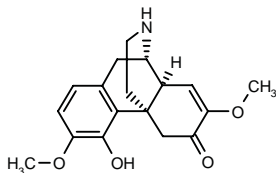
REFERENCES

1. Kukkola, P.J. et al. (Novartis AG) Sulfonylamino derivs. which inhibit matrix-degrading metalloproteinases. WO 9942443.

280357

(9α,13α,14α)-4-Hydroxy-3,7-dimethoxy-7,8-didehydro-morphinan-6-one

N-Demethylsinomenine



C18 H21 N O4; Mol wt: 315.3669

ACTION – Metabolite of the antiarthritic alkaloid sinomenine⁺ that has been shown to have up to 5-fold greater immunosuppressive activity compared to sinomenine, as well as higher water solubility. Potentially useful for treating rheumatoid arthritis, neuralgia, ankylosing spondylitis, Reiter's syndrome, Behcet's syndrome, lupus erythematosus, nephritis, psoriasis, multiple sclerosis, hepatitis, vasculitis syndrome, atherosclerosis and bronchiolitis obliterans, as well as for preventing organ or cell transplant rejection.

SOURCE – AvMax.

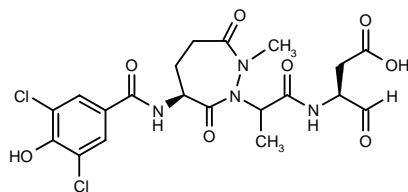
REFERENCES

1. Christians, U. and Kaever, V.W. (AvMax, Inc.) *Epimorphian cpd. and its use*. WO 9942105.

*Drug Data Rep 1998, 020(02): 0133.

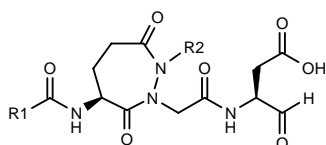
281215

N-[2-[6(*S*)-(3,5-Dichloro-4-hydroxybenzamido)-2-methyl-3,7-dioxo-1,2-diazepan-1-yl]propionyl]-L-aspart-1-al



C20 H22 Cl2 N4 O8; Mol wt: 517.3198

ACTION – Agent for the treatment of inflammatory, autoimmune, destructive bone, proliferative, infectious and degenerative disorders, a selective inhibitor of IL-1 β -converting enzyme (ICE, or caspase 1) with a K_i value of 0.9 nM and an IC_{50} value of 540 nM in an *in vitro* assay using human peripheral blood mononuclear cells (PBMCs). Other compounds from this series of 1,2-diazepane derivatives include the following:



Compound	R1	R2	Formula
281216	1-isoquinolyl	CH2Ph	C ₂₈ H ₂₇ N ₅ O ₇
281217	1-isoquinolyl	Pr	C ₂₈ H ₂₇ N ₅ O ₇
281218	3,5-(Cl)2-4-OH-Ph	Pr	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₈
281219	3,5-(Cl)2-4-OH-Ph	SO2Me	C ₁₉ H ₂₀ Cl ₂ N ₄ O ₁₀ S

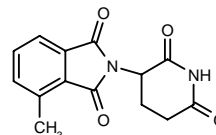
SOURCE – Vertex.

REFERENCES

1. Wannamaker, M.W. et al. (Vertex Pharmaceuticals Inc.) *1,2-Diazepane derivs. as interleukin-1 β converting enzyme inhibitors*. WO 9946248.

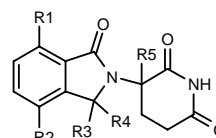
281229

2-(2,6-Dioxopiperidin-3-yl)-4-methylisoindoline-1,3-dione



C14 H12 N2 O4; Mol wt: 272.2588

ACTION – Antiinflammatory agent that acts as an inhibitor of the production of TNF- α and other inflammatory cytokines, i.e., IL-1, IL-6 and IL-12. Potentially useful in the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, graft-versus-host disease, asthma, respiratory distress syndrome and AIDS, as well as for cancer and undesirable angiogenesis. Other representative compounds from this series of 2-(2,6-dioxopiperidin-3-yl)isoindoline derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
281230	H	Et	-O-		H	C ₁₅ H ₁₄ N ₂ O ₄
281231	H	F	-O-		H	C ₁₃ H ₉ FN ₂ O ₄
281232	H	Cl	-O-		H	C ₁₃ H ₉ ClN ₂ O ₄
281233	H	CONH2	-O-		H	C ₁₄ H ₁₁ N ₃ O ₅
281234	H	OMe	-O-		H	C ₁₄ H ₁₂ N ₂ O ₅
281235	H	Me	H	H	H	C ₁₄ H ₁₄ N ₂ O ₃
281236	Me	Me	-O-		H	C ₁₅ H ₁₄ N ₂ O ₄
281237	H	N(Me)2	-O-		H	C ₁₅ H ₁₅ N ₃ O ₄
281238	H	Me	-O-		Me	C ₁₅ H ₁₄ N ₂ O ₄

SOURCE – Celgene.

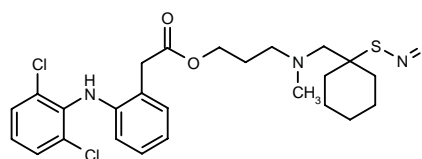
REFERENCES

1. Man, H.-W. and Muller, G.W. (Celgene Corp.) *2-(2,6-Dioxopiperidin-3-yl)isoindoline derivs., their preparation and their use as inhibitors of inflammatory cytokines*. WO 9947512.

NMI-377

279530

2-[2-(2,6-Dichlorophenylamino)phenyl]acetic acid 3-[*N*-methyl-*N*-(1-(nitrososulfanyl)cyclohexylmethyl)amino]-propyl ester



C25 H31 Cl2 N3 O3 S; Mol wt: 524.5099

Green crystals, *m.p.* 58 °C.

ACTION – Antiinflammatory agent, a nitric oxide (NO)-donating prodrug of diclofenac with comparable analgesic and antiinflammatory activity but significantly less gastrointestinal toxicity.

SOURCE – NitroMed.

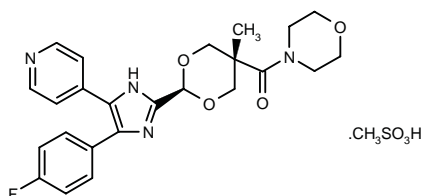
REFERENCES

1. Bandarage, U.K. et al. *NMI-377, a nitric oxide-donating diclofenac derivative with gastroprotective properties*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 81.

RPR-200765A

279791

trans-1-[2-[4-(4-Fluorophenyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-5-methyl-1,3-dioxan-5-yl]-1-(4-morpholinyl)-methanone methanesulfonate



C₂₄ H₂₅ F N₄ O₄ . C H₄ O₃ S; Mol wt: 548.5891

ACTION – Antiinflammatory agent, an analogue of SB-203580 proven to be a potent inhibitor of p38 MAP (mitogen-activated protein) kinase. Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Rhône-Poulenc Rorer.

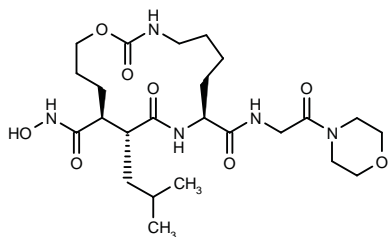
REFERENCES

1. Bamborough, P.L. et al. (Rhône-Poulenc Rorer Ltd.) *Imidazolyl-cyclic acetals*. WO 9856788.
2. McLay, I. et al. *RPR200765A, discovery of a novel P38 inhibitor*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 186.

SP-057

279490

(8*S*,11*R*,12*S*)-*N*¹²-Hydroxy-11-isobutyl-*N*⁸-[2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide



C₂₄ H₄₁ N₅ O₈; Mol wt: 527.6149

ACTION – Agent for the treatment of osteoarthritis and rheumatoid arthritis, an inhibitor of matrix metalloproteinase and TNF- α production with good oral activity in the lipopolysaccharide (LPS) mouse model of TNF- α release.

SOURCE – DuPont Pharmaceuticals.

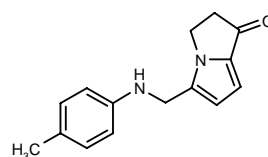
REFERENCES

1. Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Novel macrocyclic cpds. as metalloprotease inhibitors*. WO 9851665.
2. Xue, C.-B. et al. (The Du Pont Merck Pharmaceutical Co.) *Novel macrocyclic cpds. as metalloprotease inhibitors*. EP 863885, WO 9718207.
3. et al. and Voss, M. *Potent, orally active macrocyclic carbamate inhibitors of MMPS and TNF- α production*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 90.

Z-53

279678

5-(4-Methylphenylaminomethyl)-2,3-dihydro-1*H*-pyrrolizin-1-one



C₁₅ H₁₆ N₂ O; Mol wt: 240.3044

ACTION – Aminomethylpyrrolizinone with antiinflammatory and analgesic activity in mice.

SOURCE – Shenyang Pharmaceutical University, Shenyang (CN).

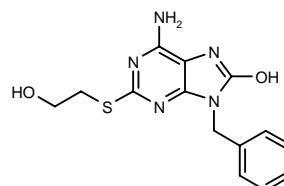
REFERENCES

1. Wang, S.J. and Zhang, S.F. *Synthesis and antiinflammatory-analgesic effects of aminomethyl-2*H*-1,2-dihydro-1-pyrrolizinone derivatives*. Chin J Med Chem 1999, 9(1): 16.

IMMUNOMODULATING AGENTS

279090

6-Amino-9-benzyl-2-(2-hydroxyethylsulfanyl)-9*H*-purin-8-ol



C₁₄ H₁₅ N₅ O₂ S; Mol wt: 317.3715

ACTION – Agent for the treatment of immunological diseases, cancer and viral infections, an inducer of the biosynthesis of interferon proven active in murine models of TNCB-induced contact hypersensitivity and arachidonic acid-induced ear hypertrophy, giving 71.2 and 94.03% inhibition of ear hypertrophy after topical application of 0.4 mg/ear, respectively. Other exemplified compounds from this series of 9*H*-purin-8-ol derivatives include the following:

ACTION – Antiinflammatory agent, a nitric oxide (NO)-donating prodrug of diclofenac with comparable analgesic and antiinflammatory activity but significantly less gastrointestinal toxicity.

SOURCE – NitroMed.

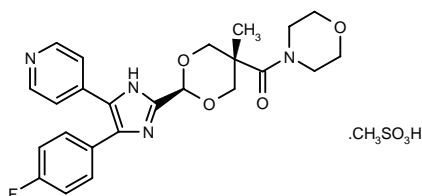
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RPR-200765A

279791

trans-1-[2-[4-(4-Fluorophenyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-5-methyl-1,3-dioxan-5-yl]-1-(4-morpholinyl)-methanone methanesulfonate



C₂₄ H₂₅ F N₄ O₄ . C H₄ O₃ S; Mol wt: 548.5891

ACTION – Antiinflammatory agent, an analogue of SB-203580 proven to be a potent inhibitor of p38 MAP (mitogen-activated protein) kinase. Potentially useful for the treatment of rheumatoid arthritis.

SOURCE – Rhône-Poulenc Rorer.

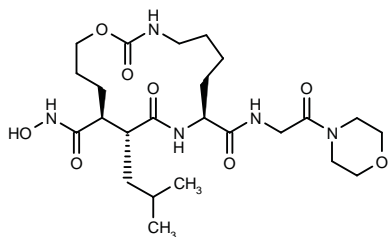
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2. McLay, I. et al. *RPR200765A, discovery of a novel P38 inhibitor*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 186.

SP-057

279490

(8*S*,11*R*,12*S*)-*N*¹²-Hydroxy-11-isobutyl-*N*⁸-[2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide



C₂₄ H₄₁ N₅ O₈; Mol wt: 527.6149

ACTION – Agent for the treatment of osteoarthritis and rheumatoid arthritis, an inhibitor of matrix metalloproteinase and TNF- α production with good oral activity in the lipopolysaccharide (LPS) mouse model of TNF- α release.

SOURCE – DuPont Pharmaceuticals.

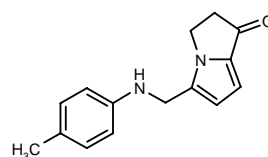
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1. Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Novel macrocyclic cpds. as metalloprotease inhibitors*. WO 9851665.
2. Xue, C.-B. et al. (The Du Pont Merck Pharmaceutical Co.) *Novel macrocyclic cpds. as metalloprotease inhibitors*. EP 863885, WO 9718207.
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Z-53

279678

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C₁₅ H₁₆ N₂ O; Mol wt: 240.3044

ACTION – Aminomethylpyrrolizone with antiinflammatory and analgesic activity in mice.

SOURCE – Shenyang Pharmaceutical University, Shenyang (CN).

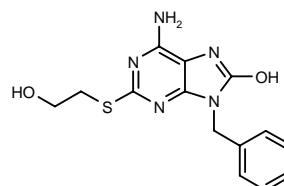
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1. Wang, S.J. and Zhang, S.F. *Synthesis and antiinflammatory-analgesic effects of aminomethyl-2*H*-1,2-dihydro-1-pyrrolizinone derivatives*. Chin J Med Chem 1999, 9(1): 16.

IMMUNOMODULATING AGENTS

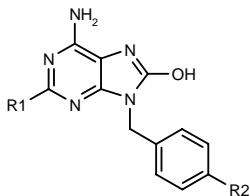
279090

6-Amino-9-benzyl-2-(2-hydroxyethylsulfanyl)-9*H*-purin-8-ol



C₁₄ H₁₅ N₅ O₂ S; Mol wt: 317.3715

ACTION – Agent for the treatment of immunological diseases, cancer and viral infections, an inducer of the biosynthesis of interferon proven active in murine models of TNCB-induced contact hypersensitivity and arachidonic acid-induced ear hypertrophy, giving 71.2 and 94.03% inhibition of ear hypertrophy after topical application of 0.4 mg/ear, respectively. Other exemplified compounds from this series of 9*H*-purin-8-ol derivatives include the following:



Compound	R1	R2	Formula
279091	SMe	H	C ₁₃ H ₁₃ N ₅ OS
279092	OC5H11	H	C ₁₇ H ₂₁ N ₅ O ₂
279093	S(CH2)3OH	H	C ₁₅ H ₁₇ N ₅ O ₂ S
279094	NHCH2CH2OMe	H	C ₁₅ H ₁₈ N ₆ O ₂
279095	OCH2CH2OMe	F	C ₁₅ H ₁₆ FN ₅ O ₃
279096	SBu	F	C ₁₆ H ₁₈ FN ₅ OS

Compounds of the invention were also found to inhibit the production of IL-4.

SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

REFERENCES

1. Kurimoto, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Japan Energy Corp.) *Novel heterocyclic cpds.* WO 9928321.

279573

Recombinant nucleic acid molecule that encodes the hepatitis C virus nonstructural protein NS5

ACTION – A nucleic acid encoding the hepatitis C virus (HCV) nonstructural protein NS5 shown to produce an immune response to NS5 and therefore useful for preparing a vaccine to protect against infection by HCV.

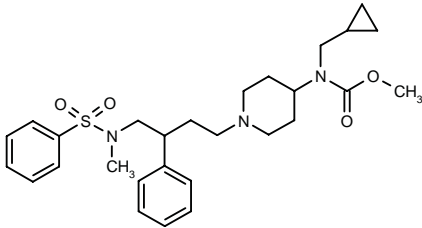
SOURCE – General Hospital.

REFERENCES

1. Wands, J. and Encke, J. (General Hospital Corporation) *Genetic immunization with nonstructural proteins of hepatitis C virus.* WO 9938880.

279782

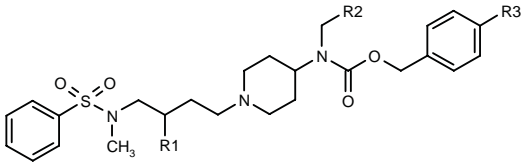
N-Cyclopropylmethyl-N-[1-[4-(N-methyl-N-phenyl-sulfonamido)-3-phenylbutyl]-4-piperidinyl]carbamic acid methyl ester



C28 H39 N3 O4 S; Mol wt: 513.6991

ACTION – Modulator of chemokine receptors such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CXCR3 and/or CXCR4, particularly CCR5, with potential in the treatment or prevention of inflammatory and immunoregulatory diseases such as asthma and allergic diseases, autoimmune diseases such as rheumatoid

arthritis and atherosclerosis, and preferably in the treatment or prevention of HIV infection/AIDS. Other specifically claimed compounds within this series of cyclic amine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
279783	Ph	cyclobutyl	H		C ₃₅ H ₄₅ N ₃ O ₄ S
279784	Ph	CH2F	H		C ₃₂ H ₄₀ FN ₃ O ₄ S
279785	Ph	CO2Me	H		C ₃₃ H ₄₁ N ₃ O ₆ S
279786	3-Cl-Ph	CO2Me	H	S	C ₃₃ H ₄₀ ClN ₃ O ₆ S
279787	2-thienyl	ethynyl	H		C ₃₁ H ₃₇ N ₃ O ₄ S ₂
279788	3-Cl-Ph	CONH2	H	S	C ₃₂ H ₃₈ ClN ₄ O ₅ S
279789	3-thienyl	vinyl	NO2		C ₃₁ H ₃₆ N ₄ O ₆ S ₂

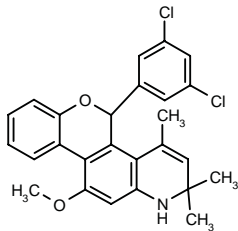
SOURCE – Merck & Co.

REFERENCES

1. Caldwell, C.G. et al. (Merck & Co., Inc.) *Cyclic amine modulators of chemokine receptor activity.* WO 9938514.

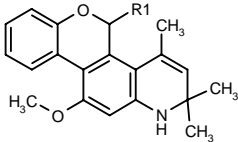
280083

5-(3,5-Dichlorophenyl)-11-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-1-benzopyrano[3,4-f]quinoline

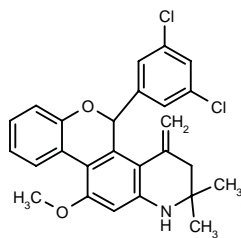


C26 H23 Cl2 N O2; Mol wt: 452.3787

ACTION – Agent for the treatment of immune, autoimmune and inflammatory diseases with high affinity and selectivity for the human glucocorticoid receptor (K_i = 200 nM) relative to the human progesterone receptor (K_i = 10,000 nM). Other specifically claimed compounds from this series of benzopyrano[3,4-f]quinolines include the following:



Compound	R1	Formula
280084	Ph	C ₂₆ H ₂₅ NO ₂
280086	allyl	C ₂₃ H ₂₅ NO ₂



280088: C₂₆ H₂₃ Cl₂ N O₂

SOURCES – Abbott; Ligand.

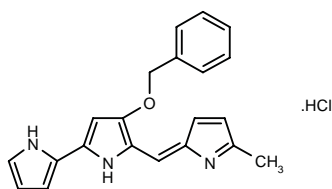
REFERENCES

1. Coughlan, M.J. et al. (Abbott Laboratories Inc.; Ligand Pharmaceuticals, Inc.) *Glucocorticoid-selective antiinflammatory agents*. WO 9941257.

PNU-168727

279826

4-Benzoyloxy-5-(5-methyl-2*H*-pyrrol-2-ylidenemethyl)-2,2'-bi-1*H*-pyrrole hydrochloride



C₂₁ H₁₉ N₃ O . HCl; Mol wt: 365.8620

ACTION – Immunosuppressive agent with improved *in vivo* activity and oral bioavailability compared to structurally related compounds. Compound exhibited ED₃₀ values of 1.7 and 5.3 mg/kg i.v. and p.o., respectively, in a delayed-type hypersensitivity assay in mice, as compared to ED₃₀ values of 0.44 and 18.7 mg/kg i.v. and p.o. for the known compound PNU-156804. Oral bioavailability in rats was 35% compared to 7% for PNU-156804. Also potentially useful for the treatment of adult T-cell leukemia-lymphoma.

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. D'Alessio, R. et al. (Pharmacia & Upjohn SpA) *Benzoyloxy prodigiosine cpds*. WO 9940069.

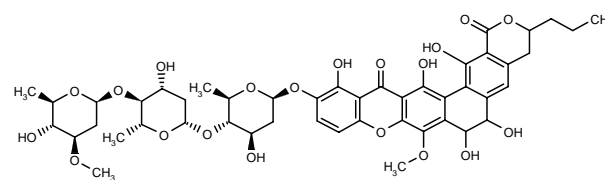
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FD-594*

235014

12-[[*O*-2,6-Dideoxy-3-*O*-methyl-β-D-glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-glucopyranosyl-(1→4)-2,6-dideoxy-β-D-glucopyranosyl]oxy]-8-methoxy-6,7,13,15,16-pentahydroxy-3-propyl-3,4,6,7-tetrahydro-pyrano[4',3':6,7]naphtho[1,2-*b*]xanthene-1,14-dione



C₄₇ H₅₆ O₂₀; Mol wt: 940.9394

Yellow powder, m.p. 199-200 °C, [α]_D²⁶ -215° (c 0.58, CHCl₃).

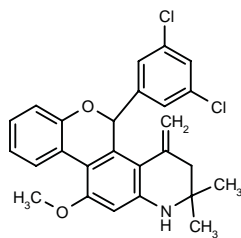
ACTION – Antineoplastic antibiotic extracted from *Streptomyces* sp. TA-0256, with moderate activity against several tumor cell lines such as human lung carcinoma A549 (IC₅₀ = 1 μg/ml), murine leukemia P388 (IC₅₀ = 0.25 μg/ml), human acute promyelocytic leukemia HL-60 (IC₅₀ = 0.10 μg/ml), murine leukemia L1210 (IC₅₀ = 0.25 μg/ml) and human cervical adenocarcinoma HeLa cells (IC₅₀ = 0.10 μg/ml). Compound also showed moderate antibacterial activity against some Gram-positive bacteria including *Staphylococcus aureus* 209P-J (MIC = 0.10 μg/ml), *Staphylococcus epidermidis* (MIC = 0.39 μg/ml) and *Bacillus subtilis* ATCC 6633 (MIC = 0.39 μg/ml).

SOURCE – Taisho.

REFERENCES

1. Kyo, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Antitumor cpd. FD-594*. JP 96041092.
2. Eguchi, T. et al. *Unique solvent-dependent atropisomerism of a novel cytotoxic naphthoxanthene antibiotic FD-594*. J Org Chem 1999, 64(15): 5371.
3. Kondo, K. et al. *Structure and biosynthesis of FD-594; a new antitumor antibiotic*. J Antibiot 1998, 51(3): 288.
4. Quiao, Y.-F. et al. *Isolation and characterization of a new pyrano[4',3':6,7]-naphtho[1,2-b]xanthene antibiotic FD-594*. J Antibiot 1998, 51(3): 282.

*Identified compound **FD-594** published without structure Drug Data Rep 1996, 018(06): 0571.



280088: C₂₆ H₂₃ Cl₂ N O₂

SOURCES – Abbott; Ligand.

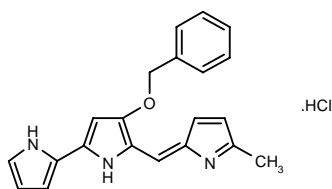
REFERENCES

1. Coughlan, M.J. et al. (Abbott Laboratories Inc.; Ligand Pharmaceuticals, Inc.) *Glucocorticoid-selective antiinflammatory agents*. WO 9941257.

PNU-168727

279826

4-Benzyloxy-5-(5-methyl-2*H*-pyrrol-2-ylidenemethyl)-2,2'-bi-1*H*-pyrrole hydrochloride



C₂₁ H₁₉ N₃ O . HCl; Mol wt: 365.8620

ACTION – Immunosuppressive agent with improved *in vivo* activity and oral bioavailability compared to structurally related compounds. Compound exhibited ED₃₀ values of 1.7 and 5.3 mg/kg i.v. and p.o., respectively, in a delayed-type hypersensitivity assay in mice, as compared to ED₃₀ values of 0.44 and 18.7 mg/kg i.v. and p.o. for the known compound PNU-156804. Oral bioavailability in rats was 35% compared to 7% for PNU-156804. Also potentially useful for the treatment of adult T-cell leukemia-lymphoma.

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. D'Alessio, R. et al. (Pharmacia & Upjohn SpA) *Benzyloxy prodigiosine cpds*. WO 9940069.

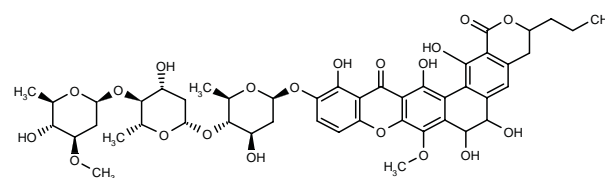
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FD-594*

235014

12-[[*O*-2,6-Dideoxy-3-*O*-methyl-β-D-glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-glucopyranosyl-(1→4)-2,6-dideoxy-β-D-glucopyranosyl]oxy]-8-methoxy-6,7,13,15,16-pentahydroxy-3-propyl-3,4,6,7-tetrahydro-pyrano[4',3':6,7]naphtho[1,2-*b*]xanthene-1,14-dione



C₄₇ H₅₆ O₂₀; Mol wt: 940.9394

Yellow powder, m.p. 199-200 °C, [α]_D²⁶ -215° (c 0.58, CHCl₃).

ACTION – Antineoplastic antibiotic extracted from *Streptomyces* sp. TA-0256, with moderate activity against several tumor cell lines such as human lung carcinoma A549 (IC₅₀ = 1 μg/ml), murine leukemia P388 (IC₅₀ = 0.25 μg/ml), human acute promyelocytic leukemia HL-60 (IC₅₀ = 0.10 μg/ml), murine leukemia L1210 (IC₅₀ = 0.25 μg/ml) and human cervical adenocarcinoma HeLa cells (IC₅₀ = 0.10 μg/ml). Compound also showed moderate antibacterial activity against some Gram-positive bacteria including *Staphylococcus aureus* 209P-J (MIC = 0.10 μg/ml), *Staphylococcus epidermidis* (MIC = 0.39 μg/ml) and *Bacillus subtilis* ATCC 6633 (MIC = 0.39 μg/ml).

SOURCE – Taisho.

REFERENCES

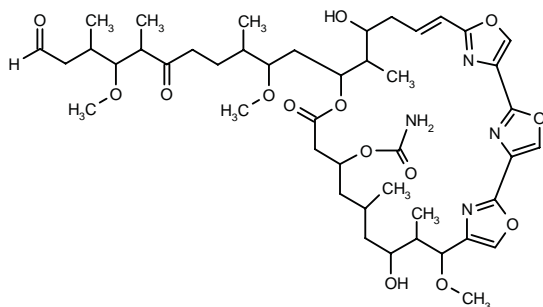
1. Kyo, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Antitumor cpd. FD-594*. JP 96041092.
2. Eguchi, T. et al. *Unique solvent-dependent atropisomerism of a novel cytotoxic naphthoxanthene antibiotic FD-594*. J Org Chem 1999, 64(15): 5371.
3. Kondo, K. et al. *Structure and biosynthesis of FD-594; a new antitumor antibiotic*. J Antibiot 1998, 51(3): 288.
4. Quiao, Y.-F. et al. *Isolation and characterization of a new pyrano[4',3':6,7]-naphtho[1,2-b]xanthene antibiotic FD-594*. J Antibiot 1998, 51(3): 282.

*Identified compound **FD-594** published without structure Drug Data Rep 1996, 018(06): 0571.

HA-1

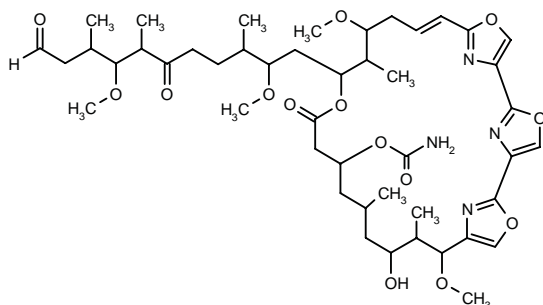
279613

16-(Carbamoyloxy)-20-(2,8-dimethoxy-6,11-dioxo-3,7,9-trimethylundecyl)-12,22-dihydroxy-10-methoxy-11,14,21-trimethyl-3,7,19,27-tetraoxa-29,30,31-triazatetracyclo[24.2.1.1^{2,5}.1^{6,9}]hentriaconta-1(28),2(31),4,6(30),8,24,26(29)-heptaen-18-one



C45 H66 N4 O14; Mol wt: 887.0304

ACTION – Antineoplastic agent, a cytotoxic macrolide derived from kabiramide B with potent *in vitro* cytotoxicity against murine leukemia P388 ($IC_{50} = 0.010 \mu M$), and particularly against solid tumors such as human lung carcinoma A549, human colon carcinoma HT-29 and human melanoma MEL-28 ($IC_{50} = 0.001$, 0.001 and $0.001 \mu M$, respectively). Another related compound from this series of cytotoxic tris(oxazole)-containing macrolides is:



TH-2 [279614]: C46 H68 N4 O14

SOURCE – Instituto Biomar.

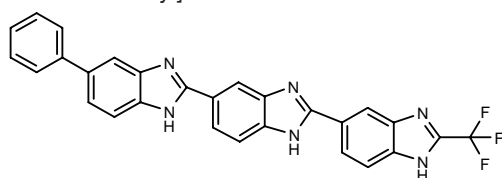
REFERENCES

1. Higa, T. et al. (Instituto Biomar SA) *New cytotoxic tris(oxazole)-containing macrolides*. WO 9937653.

DNA-INTERCALATING DRUGS

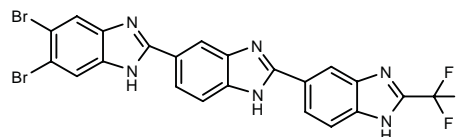
280022

5-Phenyl-2-[2-(2-trifluoromethyl-1*H*-benzimidazol-5-yl)-1*H*-benzimidazol-5-yl]-1*H*-benzimidazole



C28 H17 F3 N6; Mol wt: 494.4783

ACTION – Antineoplastic agent with topoisomerase I-inhibitory activity ($IC_{50} < 0.01 \mu M$) and cytotoxicity against a broad range of human cancer cell lines including lymphoblast RPMI 8042 ($IC_{50} = 0.02 \mu M$), lymphoma U937 ($IC_{50} = 0.006 \mu M$), breast carcinoma MDA-MB-435 ($IC_{50} = 0.08 \mu M$), prostate cancer PC-3 ($IC_{50} = 0.06 \mu M$) and epidermoid carcinoma KB3-1 cells ($IC_{50} = 0.01 \mu M$). Another representative compound from this series of benzimidazole derivatives is:



280023: C22 H11 Br2 F3 N6

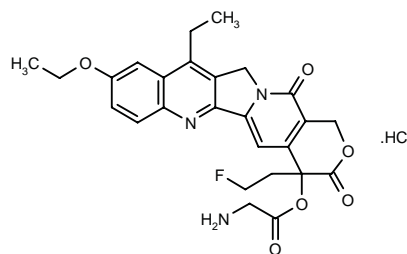
SOURCE – State University of New Jersey, Piscataway, NJ (US).

REFERENCES

1. Lavoie, E.J. et al. (State University of New Jersey) *Heterocyclic topoisomerase poisons*. WO 9941241.

280346

4-(Glycyloxy)-9-ethoxy-11-ethyl-4-(2-fluoroethyl)-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14-dione hydrochloride



C26 H26 F N3 O6 . HCl; Mol wt: 531.9653

ACTION – Water-soluble fluoroethylcamptothecin derivative with potent antineoplastic activity and low toxicity. It was at least as effective as irinotecan hydrochloride against sarcoma 180 tumors in mice and, in contrast to irinotecan, it showed significant activity and low toxicity in mice bearing colon 26 tumors. Furthermore, the new camptothecin derivative was much less effective than irinotecan in inhibiting acetylcholinesterase and is therefore expected to have a reduced liability for gastrointestinal toxicity, i.e., diarrhea.

SOURCE – Kyorin.

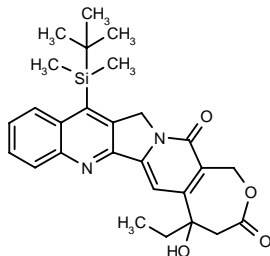
REFERENCES

1. Asahina, Y. and Oomori, Y. (Kyorin Pharmaceutical Co., Ltd.) *Water-soluble fluoroethylcamptothecin deriv. and process for production thereof*. US 5942518, WO 9641806.

DB-81

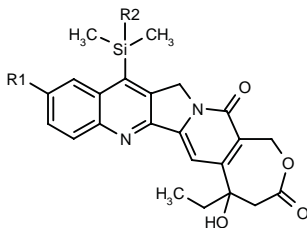
279494

12-(*tert*-Butyldimethylsilyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione



C27 H32 N2 O4 Si; Mol wt: 476.6458

ACTION – Antineoplastic agent, a camptothecin derivative with *in vitro* cytotoxic activity against breast carcinoma MDA-MB-435 cells (IC₅₀ = 20-100 nM) and improved lipophilicity and stability in mouse and human blood compared to parent compound. Other homosilatecan derivatives include the following:



Compound	R1	R2	Formula
DB-38 [279493]	NH2	Me	C ₂₄ H ₂₇ N ₃ O ₄ Si
DB-90 [279495]	NH2	t-Bu	C ₂₇ H ₃₃ N ₃ O ₄ Si
DB-91 [279496]	OH	t-Bu	C ₂₇ H ₃₂ N ₂ O ₅ Si

SOURCES – University of Kentucky, Lexington, KY (US); Tigen Pharmaceuticals.

REFERENCES

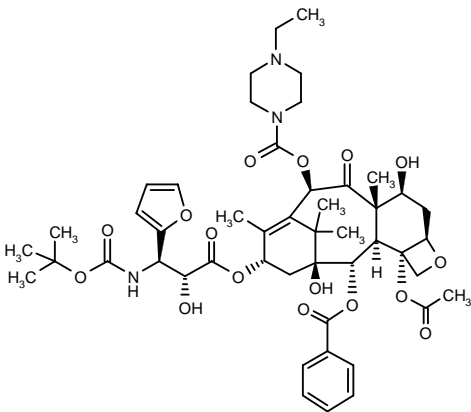
1. Bom, D. et al. *Novel A,B,E-ring-modified camptothecins displaying high lipophilicity and markedly improved human blood stabilities.* J Med Chem 1999, 42(16): 3018.

ANTIMITOTIC DRUGS

279225

4-Ethyl-1-piperazinecarboxylic acid (1*S*,2*S*,3*R*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-4-acetoxy-2-benzoyloxy-15-[3(*R*)-(tert-butoxycarbonylamino)-3-(2-furyl)-2(*R*)-hydroxypropionyloxy]-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-en-12-yl ester

[2*aR*,4*S*,4*aS*,6*R*,9*S*(α *R*, β *R*),11*S*,12*S*,12*aR*,12*bS*]-12b-Acetoxy-12-benzoyloxy-9-[3-(tert-butoxycarbonylamino)-3-(2-furyl)-2-hydroxypropionyloxy]-6-(4-ethylpiperazin-1-ylcarbonyloxy)-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C48 H63 N3 O16; Mol wt: 938.0307

ACTION – Antineoplastic agent, a taxane derivative with higher antitumor activity compared to paclitaxel against KB cells (GI₅₀ = 0.23 ng/ml vs. 1.3 ng/ml for paclitaxel) and improved water solubility (1574 µg/ml vs. 0.4 µg/ml for paclitaxel).

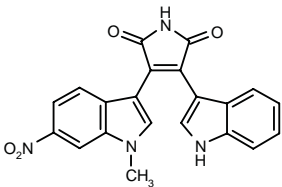
SOURCE – Yakult Honsha.

REFERENCES

1. Shimizu, H. et al. (Yakult Honsha Co., Ltd.) *Taxane derivs.* WO 9932473.

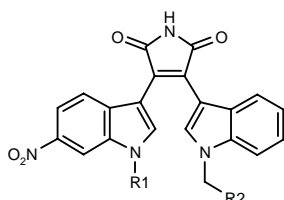
281274

3-(1*H*-Indol-3-yl)-4-(1-methyl-6-nitro-1*H*-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione



C21 H14 N4 O4; Mol wt: 386.3656

ACTION – Antiproliferative agent that inhibits cell division in the G2/M phase of the cell cycle and is particularly useful for the treatment of solid tumors. It exhibited potent activity against human breast carcinoma MDA-MB-435, human colon adenocarcinoma SW480 and human colon carcinoma HCT-116 cell lines *in vitro*, with respective IC₅₀ values of 0.03, 0.17 and 0.20 μ M. Other specifically claimed substituted bisindolymaleimides are:



Compound	R1	R2	Formula
281275	H	H	C ₂₁ H ₁₄ N ₄ O ₄
281276	Me	OH	C ₂₂ H ₁₆ N ₄ O ₅

SOURCE – Roche.

REFERENCES

1. Dhingra, U.H. et al. (F. Hoffmann-La Roche AG) *Subst. bisindolymaleimides for the inhibition of cell proliferation*. WO 9947518.

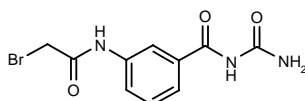
MF-191

279594

N-[3-(Bromoacetamido)benzoyl]urea

N-(Aminocarbonyl)-3-(bromoacetamido)benzamide

3-BAABU



C10 H10 Br N3 O3; Mol wt: 300.1110

ACTION – Antineoplastic agent, an inhibitor of tubulin polymerization that acts by directly binding to tubulin units and preventing the formation of mitotic spindles. Compound showed strong cytotoxic activity, inducing irreversible mitotic arrest and subsequent apoptosis in human leukemia CEM, human biphenotypic leukemia SP, human prostate carcinoma PC-3, murine melanoma B16 and murine lymphoma/leukemia EL4 cells, with ID₅₀ values of 0.04-0.22 μ M. It did not show cytotoxicity or mitosis-blocking effects in normal human lymphocytes, proliferating 3T3 fibroblasts or proliferating myocardial cells. *In vivo* in leukemia P388-bearing mice, compound reduced ascitic tumor burden with an ED₅₀ of 27 μ mol/kg i.p. and a therapeutic index of 3.4, higher than that of vinblastine and paclitaxel (2.0 and 1.3, respectively). Kinetic studies with compound indicated rapid uptake by proliferating cells and irreversibility of its effect.

SOURCES – Cytoskeleton; Mount Sinai School of Medicine, New York, NY (US).

REFERENCES

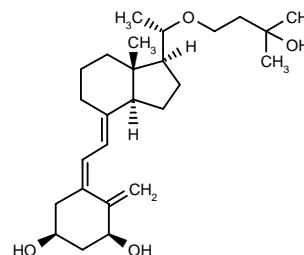
- Davis, A. and Middleton, K. *HTS assay for tubulin ligands with anticancer properties*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 172.
- Jiang, J.-D. et al. *Synthesis, cancericidal and antimicrotubule activities of 3-(haloacetamido)-benzoylureas*. *Anti-Cancer Drug Des* 1998, 13(7): 735.
- Jiang, J.D. et al. *3-Bromoacetyl amino benzoylurea (3-BAABU), a new anti-microtubule cancericidal agent applied in cytogenetic analysis in hematology*. *Biomed Pharmacother* 1998, 52(6): 270.
- Jiang, J.D. et al. *Inhibition of microtubule assembly in tumor cells by 3-bromoacetyl amino benzoylurea, a new cancericidal compound*. *Cancer Res* 1998, 58(10): 2126.

HORMONAL AGENTS

279205

1 α ,25-Dihydroxy-3-epi-22-oxavitamin D₃

20(*S*)-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5(*Z*),7(*E*),10(19)-trien-1(*S*),3(*S*)-diol



C26 H42 O4; Mol wt: 418.6138

ACTION – Agent for the treatment of cancer, inflammatory disorders, psoriasis and hyperparathyroidism, a representative compound from a series of 3-epi-22-oxavitamin D derivatives.

SOURCE – Chugai.

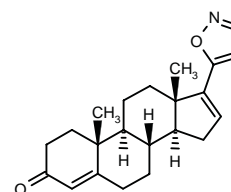
REFERENCES

- Hatayama, N. and Iwabuchi, Y. (Chugai Pharmaceutical Co. Ltd.) *Vitamin D derivs. and their preparation method*. JP 99171859.

L-39

255756

17-(5-Isoxazolyl)androsta-4,16-dien-3-one



C22 H27 N O2; Mol wt: 337.4603

ACTION – Potent inhibitor of androgen synthesis, an androstene derivative proven to noncompetitively inhibit human testicular microsomal 17 α -hydrolase/C_{17,20}-lyase (K_i = 22 nM) and human prostatic microsomal 5 α -reductase (K_i = 27.55 nM). In prostate cancer LNCaP cell cultures, compound (5 μ M) inhibited both testosterone- and dihydrotestosterone-stimulated cell growth and showed antiandrogenic activity by displacing [³H]-R-1881 binding from androgen receptors. *In vivo* in nude mice bearing androgen-dependent human prostate cancer PC-82 xenografts or SCID mice bearing LNCaP xenografts, compound (50 mg/kg/day for 28 days) significantly decreased tumor growth and wet weight to a similar extent as castration or the antiandrogen flutamide. Potentially useful for the treatment of prostate cancer.

SOURCE – University of Maryland, Baltimore, MD (US).

REFERENCES

1. Brodie, A. and Ling, Y. (University of Maryland) *Androgen synthesis inhibitors*. WO 9833506.

2. Ling, Y. et al. 17-Imidazolyl, pyrazolyl, and isoxazolyl androstene derivatives, novel steroidal inhibitors of human cytochrome C17,20-lyase (P45017alpha). J Med Chem 1997, 40(20): 3297.

3. Long, B.J. et al. *In vitro* and *in vivo* inhibition of LNCaP prostate cancer cell growth by novel inhibitors of androgen synthesis. Proc Amer Assoc Cancer Res 1999, 40: Abst 423.

4. Nnane, I.P. et al. *The effects of 17-(5'isoxazolyl)androsta-4,16-dien-3-one in vitro and on human prostate cancer xenographs in nude mice*. 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P1-619.

CANCER IMMUNOTHERAPY

TASONERMIN

Prop INN

256899

1-157-Tumor necrosis factor α -1a (human)

ACTION – Immunomodulating agent, a cytokine belonging to the TNF- α family with antitumor activity.

INDICATION – Adjunct to surgery for the subsequent removal of tumors so as to prevent or delay amputation, or for the palliative treatment of nonresectable soft tissue sarcoma of the limbs in combination with melphalan via mild hyperthermic isolated limb perfusion.

PRESENTATION – Powder and solvent for solution for infusion (isolated limb perfusion), 1 mg.

PROPRIETARY NAME – Beromun (EU).

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Boehringer Ingelheim's TNFalpha-1a launched in Europe for soft tissue sarcoma. DailyDrugNews.com (Daily Essentials) 1999, Sept 16.

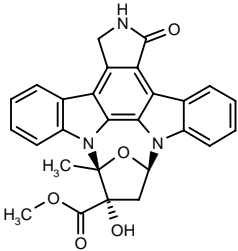
2. European Commission issues first approval for tasonermin. DailyDrugNews.com (Daily Essentials) 1999, June 8.

3. Proposed international nonproprietary names (Prop. INN): List 76. WHO Drug Inf 1996, 10(4): 217.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

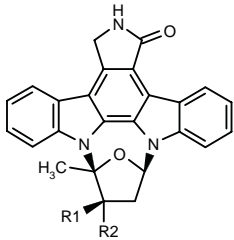
278730^{1,2}

10(S)-Hydroxy-9(S)-methyl-1-oxo-9,12(R)-epoxy-2,3,9,10,11,12-hexahydro-1H-diindolo[1,2,3-fg:3',2',1'-kl]-pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid methyl ester



C27 H21 N3 O5; Mol wt: 467.4789

ACTION – Agent for the treatment of cancer and neurodegenerative disorders, an inhibitor of tyrosine kinases such as protein kinase C (PKC; IC₅₀ = 114 nM), trkA tyrosine kinase (IC₅₀ = 1.4 nM) and vascular endothelial growth factor (VEGF) receptor kinase (IC₅₀ = 19 nM). Compound also possesses positive effects on the function and/or survival of trophic factor-responsive cells, as demonstrated by its ability to promote choline acetyltransferase (ChAT) activity in rat embryonic spinal cord cultures. Other compounds from this series of 3'-epimeric K-252A derivatives include the following:



Compound	R1	R2	Formula
278731 ¹	CH2OH	H	C ₂₆ H ₂₁ N ₃ O ₃
278732 ¹	CH2OH	OH	C ₂₆ H ₂₁ N ₃ O ₄
278733 ¹	Me	OH	C ₂₆ H ₂₁ N ₃ O ₃

SOURCES – Cephalon; Kyowa Hakko.

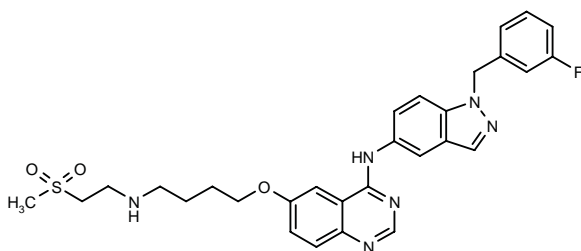
REFERENCES

1. Hudkins, R.L. and Gingrich, D.E. (Cephalon, Inc.;Kyowa Hakko Kogyo Co., Ltd.) 3'-Epimeric K-252A derivs. WO 9933836.

2. Gingrich, D.E. et al. *Synthesis of 3'-epi-K252A*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 202.

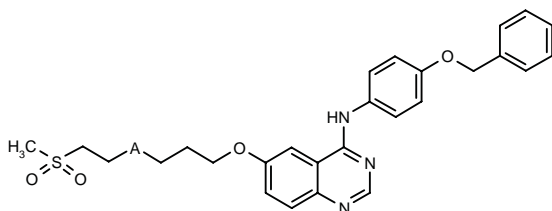
278875

N-[1-(3-Fluorobenzyl)-1*H*-indazol-5-yl]-*N*-[6-[4-[2-(methylsulfonyl)ethylamino]butoxy]-4-quinazolinyl]amine



C29 H31 F N6 O3 S; Mol wt: 562.6669

ACTION – Antineoplastic agent, a potent inhibitor of protein tyrosine kinases, particularly c-erbB-2 protein tyrosine kinase ($IC_{50} < 0.10 \mu M$). Compound inhibited the growth of human breast epithelial HB4a cells transformed by overexpression of c-erbB-2 ($IC_{50} < 5 \mu M$), while it showed less inhibitory activity on the growth of HB4a cells transfected with *ras* ($IC_{50} = 5-25 \mu M$). Antiproliferative activity was also demonstrated against naturally occurring epidermal growth factor (EGF) receptor- or c-erbB-2-overexpressing human tumor cell lines such as breast BT474 ($IC_{50} < 5 \mu M$), head and neck HN5 ($IC_{50} < 5 \mu M$) and gastric N87 ($IC_{50} < 5 \mu M$) cell lines. Also claimed for the treatment of psoriasis. Other representative bicyclic heteroaromatic compounds include the following:



Compound	A	Formula
278876	-NHCH2-	C ₂₈ H ₃₂ N ₄ O ₄ S
278877	-N(Me)-	C ₂₈ H ₃₂ N ₄ O ₄ S

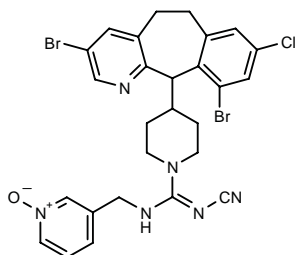
SOURCE – Glaxo Wellcome.

REFERENCES

1. Cockerill, G.S. and Lackey, K.E. (Glaxo Group Ltd.) *Heterocyclic cpds.* WO 9935132.

278886

N'-Cyano-4-(8-chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-*N*-(1-oxido-pyridin-3-ylmethyl)piperidine-1-carboximidine



C27 H25 Br2 Cl N6 O; Mol wt: 644.7965

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase ($IC_{50} = 0.0017 \mu M$) and of the farnesylation of the oncogene protein Ras. A specifically claimed compound within a series of tricyclic *N*-cyanoimine derivatives.

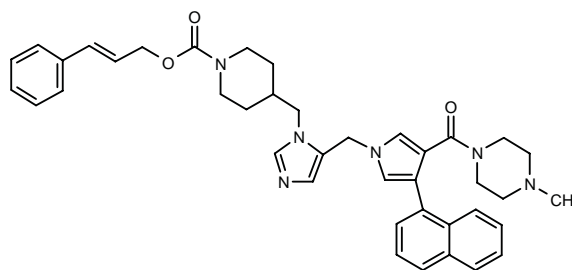
SOURCE – Schering-Plough.

REFERENCES

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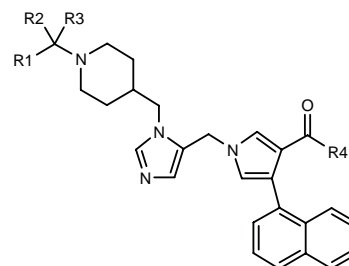
279714

4-[5-[3-(4-Methylpiperazin-1-ylcarbonyl)-4-(1-naphthyl)-1*H*-pyrrol-1-ylmethyl]-1*H*-imidazol-1-ylmethyl]piperidine-1-carboxylic acid 3-phenylprop-2(*E*)-enyl ester



C40 H44 N6 O3; Mol wt: 656.8266

ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase and the farnesylation of Ras. Compound exhibited IC_{50} values of 0.0033 and 0.007 μM when tested against recombinant farnesyltransferase using H- and K-Ras as the substrate, respectively. In addition, it was shown to inhibit the farnesylation of H- and K-Ras in *ras*-transformed Rat2 fibroblast cells with IC_{50} values of 0.0125 and 1 μM , respectively. Within this series of piperidine derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
279715	OCH2Ph	-O-		4-morpholinyl	C ₃₇ H ₃₉ N ₅ O ₄
279716	OCH2Ph	-O-		N(Me)CH2CH2OMe	C ₃₇ H ₄₁ N ₅ O ₄
279717	4-F-PhCH2O	-O-		N(Me)CH2CH2OMe	C ₃₇ H ₄₀ FN ₅ O ₄
279718	1,2,3,4-tetrahydro-2-isoquinolinyl	-O-		N(Me)CH2CH2OMe	C ₃₉ H ₄₄ N ₆ O ₃
279719	OCH2Ph	-O-		4-Me-1-Piz	C ₃₈ H ₄₂ N ₆ O ₃
279720	4-F-PhCH2O	-O-		4-Me-1-Piz	C ₃₈ H ₄₁ FN ₆ O ₃
279721	2-Naph	-O-		4-Me-1-Piz	C ₄₁ H ₄₂ N ₆ O ₂
279722	4-Ph-Ph	H	H	4-Me-1-Piz	C ₄₃ H ₄₆ N ₆ O
279723	4-(PhO)-Ph	H	H	4-Me-1-Piz	C ₄₃ H ₄₆ N ₆ O ₂

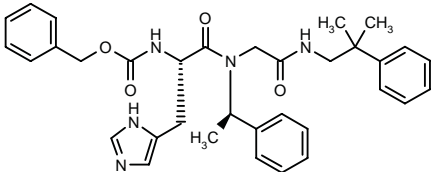
SOURCE – LG Chem.

REFERENCES

1. Shin, Y.S. et al. (LG Chem Ltd.) *Farnesyl transferase inhibitors having a piperidine structure and process for preparation thereof.* WO 9938862.

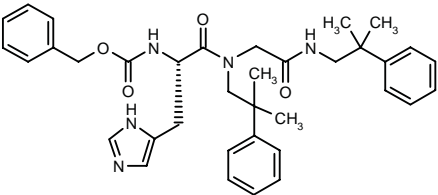
279903

N²-[N-(Benzyloxycarbonyl)-L-histidyl]-N¹-(2-methyl-2-phenylpropyl)-N²-[1(R)-phenylethyl]glycinamide



C34 H39 N5 O4; Mol wt: 581.7131

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC₅₀ = 0.001 μM) proven to prevent H-Ras farnesylation in NIH 3T3 cells with a minimal effective dose (MED) of 0.01 μM. Another compound from this series of histidyl-(N-benzyl-glycinamides) is:



279904: C36 H43 N5 O4

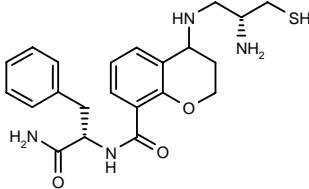
SOURCE – Warner-Lambert.

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2. Shuler, K.R. et al. *Structure-activity studies on two histidyl-(N-benzylglycinamide) RAS farnesyl transferase inhibitors.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 213.

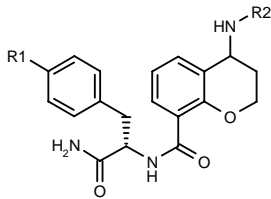
279952

N-[1(S)-Carbamoyl-2-phenylethyl]-4-[2(R)-amino-3-sulfanylpropylamino]-3,4-dihydro-2H-1-benzopyran-8-carboxamide



C22 H28 N4 O3 S; Mol wt: 428.5542

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. Other specifically claimed condensed heterocyclic compounds include the following:



Compound	R1	R2	Formula
279953	OH	(R)-CH ₂ CH(NH ₂)CH ₂ SH	C ₂₂ H ₂₈ N ₄ O ₃ S
279954	OH	(R)-COCH(NH ₂)CH ₂ SH	C ₂₂ H ₂₈ N ₄ O ₃ S
279955	Cl	1-(4-NO ₂ -PhCH ₂)-5-imidazolyl-CH ₂	C ₃₀ H ₂₉ ClN ₆ O ₅
279956	Cl	1-(4-F-PhCH ₂)-5-imidazolyl-CH ₂	C ₃₀ H ₂₉ ClF ₂ N ₅ O ₃
279958	Cl	1-(4-Me-PhCH ₂)-5-imidazolyl-CH ₂	C ₃₁ H ₃₂ ClN ₅ O ₃
279959	Cl	1-[4-(t-BuCONH)-PhCH ₂]-5-imidazolyl-CH ₂	C ₃₅ H ₃₉ ClN ₆ O ₄
279960	Br	1-(4-Ph-Ph)-5-imidazolyl-CH ₂	C ₃₅ H ₃₂ BrN ₅ O ₃

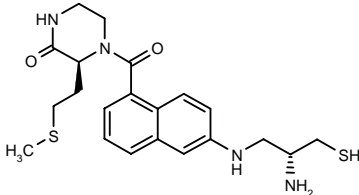
SOURCE – Rhône-Poulenc Rorer.

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1. Baudoin, B. et al. (Rhône-Poulenc Rorer SA) *Condensed heterocyclic system derivs., preparation, pharmaceutical compsns. containing them.* FR 2774987, WO 9941248.

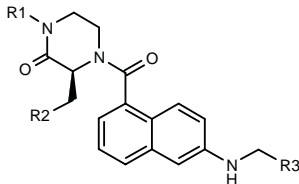
280057

4-[6-[2(R)-Amino-3-sulfanylpropylamino]naphthalen-1-ylcarbonyl]-3(S)-[2-(methylsulfanyl)ethyl]piperazin-2-one



C21 H28 N4 O2 S2; Mol wt: 432.6102

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. Other specifically claimed compounds from this series of di-substituted naphthyl derivatives include the following:



Compound	R2	R2	R3	Formula
280058	H	OH	(R)-CH(NH ₂)CH ₂ SH	C ₁₉ H ₂₄ N ₄ O ₃ S
280059	H	Pr	1-(4-CN-PhCH ₂)-5-imidazolyl	C ₃₁ H ₃₂ N ₆ O ₂
280060	CH ₂ Ph	CH ₂ SMe	(R)-CH(NH ₂)CH ₂ SH	C ₂₈ H ₃₄ N ₄ O ₂ S ₂
280061	H	CH ₂ CONH ₂	(R)-CH(NH ₂)CH ₂ SH	C ₂₁ H ₂₇ N ₅ O ₃ S
280062	H	CH ₂ SMe	3-Pyr	C ₂₄ H ₂₆ N ₄ O ₂ S

SOURCE – Rhône-Poulenc Rorer.

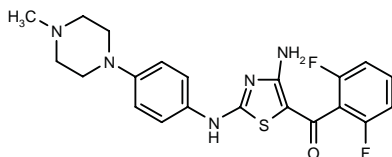
REFERENCES

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AG-12275*

276485

1-[4-Amino-2-[4-(4-methyl-1-piperazinyl)phenylamino]-thiazol-5-yl]-1-(2,6-difluorophenyl)methanone



C21 H21 F2 N5 O S; Mol wt: 429.4929

ACTION – Antineoplastic agent, an inhibitor of cyclin-dependent kinase 4 (CDK4/cyclinD; $K_i = 3.3$ nM) with good selectivity over other kinases including CDK2/cyclin A, CDK1/cyclin B, protein kinase A, protein kinase C and ERK2 (MAP kinase p42/44) ($K_i = 0.22, 0.32, > 20, 11.2$ and > 100 μ M, respectively). In human colon carcinoma HCT-111 cells, it caused accumulation in the G1 phase of the cell cycle and inhibited cell growth with an IC_{50} of 0.3 μ M. *In vivo* in HCT-116-bearing mice, compound significantly delayed tumor growth at doses of 25-100 mg/kg i.p.

SOURCE – Agouron (Warner-Lambert).

REFERENCES

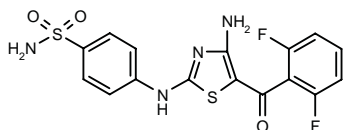
1. Chong, W.K.M. et al. (Agouron Pharmaceuticals, Inc.) *4-Aminothiazole derivs., their preparation and their use as inhibitors of cyclin-dependent kinases*. WO 9921845.
2. Chong, W.K.M. et al. *Unique cyclin-dependent kinase (CDK) inhibitors at the ATP-site*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 315.

*Identified compound **276485** (see **276482**) Drug Data Rep 1999, 021(06): 0549.

AG-12286*

276482

4-[4-Amino-5-(2,6-difluorobenzoyl)thiazol-2-ylamino]-benzenesulfonamide



C16 H12 F2 N4 O3 S2; Mol wt: 410.4238

ACTION – Antineoplastic agent, a broad-spectrum cyclin-dependent kinase (CDK) inhibitor active against CDK4/D, CDK2/A and CDK1/B ($K_i = 12, 5.7$ and 2.2 nM, respectively) and showing high selectivity over other protein kinases including protein kinase C, cAMP-dependent protein kinase, ERK2 (MAP kinase p42/44) and vascular endothelial growth factor (VEGF) receptor tyrosine kinase ($K_i = 11,500, > 20,000, > 50,000$ and > 5000 nM, respectively). Compound caused the accumulation of human colon carcinoma HCT-116 and breast carcinoma MDA-MB-453 cells in the G1, G2 and S phases of the cell cycle, and it showed antiproliferative activity against HCT-116 cells ($IC_{50} = 0.25$ μ M).

SOURCE – Agouron (Warner-Lambert).

REFERENCES

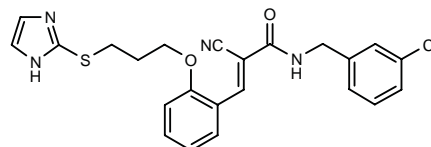
1. Chong, W.K.M. et al. (Agouron Pharmaceuticals, Inc.) *4-Aminothiazole derivs., their preparation and their use as inhibitors of cyclin-dependent kinases*. WO 9921845.
2. Chong, W.K.M. et al. *Unique cyclin-dependent kinase (CDK) inhibitors at the ATP-site*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 315.
3. Duvadie, R.K. et al. *Novel ATP-site cyclin-dependent kinase (CDK) inhibitors: Selective CDK inhibitors*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 214.

*Identified compound **276482** Drug Data Rep 1999, 021(06): 0549.

AGR-129

279901

N-(3-Chlorobenzyl)-2-cyano-3-[2-[3-(1H-imidazol-2-ylsulfanyl)propoxy]phenyl]-2(E)-propenamide



C23 H21 Cl N4 O2 S; Mol wt: 452.9639

ACTION – Antineoplastic agent, a potent, nonpeptide, nonsulfhydryl protein farnesyltransferase inhibitor ($IC_{50} = 1.8$ μ M) with 33-fold selectivity over geranylgeranyltransferase type I ($IC_{50} = 59.3$ μ M). The kinetics of enzyme inhibition demonstrated that compound is a pure competitive inhibitor of farnesyltransferase with respect to Ras protein and a mixed competitive inhibitor with respect to farnesyl pyrophosphate. In intact cells, compound at 120 μ M completely inhibit Ras farnesylation but did not affect Rap-1 geranylgeranylation. It was able to inhibit the growth of colon carcinoma LIM1899 cells expressing a mutant K-ras, NIH3T3 cells and v-H-ras-transformed NIH3T3 cells with IC_{50} values of 100, 186 and 152 μ M, respectively, as well as colony formation of v-H-ras-transformed NIH3T3 cells in soft agar (75% inhibition at 100 μ M).

SOURCE – Hebrew University, Jerusalem (IL).

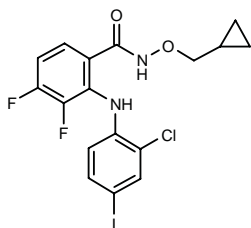
REFERENCES

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PD-184352*

272343

2-(2-Chloro-4-iodophenylamino)-*N*-(cyclopropylmethoxy)-3,4-difluorobenzamide



C17 H14 Cl F2 I N2 O2; Mol wt: 478.6586

ACTION – Antineoplastic agent, a potent and selective MEK1 inhibitor ($IC_{50} = 17$ nM) able to inhibit the *in vitro* growth of colon carcinoma cell lines ($IC_{50} = 0.12$ - 0.18 μ M). *Ex vivo* experiments demonstrated that compound (150 mg/kg p.o.) completely suppressed MAP kinase phosphorylation in colon 26 carcinoma cells implanted s.c. in mice; in these animals, compound given orally at doses of 48-200 mg/kg b.i.d. for 14 days inhibited tumor growth by 53-79%. It was also able to inhibit the growth of human colon carcinoma HT-29 xenografts, but not of P388 leukemia cells implanted i.p. in mice, indicating that antineoplastic activity is correlated with MEK-inhibitory activity.

SOURCE – Warner-Lambert.

REFERENCES

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2. Bridges, A.J. (Warner-Lambert Co.) Method of treating or preventing septic shock by administering a MEK inhibitor. WO 9837881.
3. Barrett, S.D. et al. *N*-Alkoxy-2-(4-iodo-phenylamino)-benzamides: *O*-Alkyl benzhydroxamate esters as a novel class of potent and long-acting *in vitro* MEK inhibitors. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 203.
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5. Przybranowski, S.A. et al. The use of *ex vivo* pharmacodynamic endpoints to optimize analog selection of MEK inhibitors and identify sensitive tumors. Proc Amer Assoc Cancer Res 1999, 40: Abst 784.
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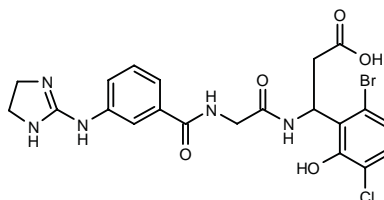
*Identified compound **272343** Drug Data Rep 1999, 021(03): 0270.

ANGIOGENESIS INHIBITORS

SC-72115

279595

N-[3-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzoyl]glycyl-3-(6-bromo-3-chloro-2-hydroxyphenyl)- β -alanine



C21 H21 Br Cl N5 O5; Mol wt: 538.7839

ACTION – Antiangiogenic agent, an $\alpha_5\beta_3$ integrin receptor antagonist with oral activity and proven to increase the efficacy of other chemotherapeutics such as cisplatin in animal models of cancer.

SOURCE – Searle.

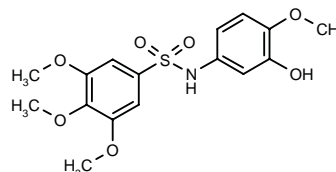
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2. Ruminski, P.G. et al. *Peptidomimetic antagonists of the alphavbeta3 integrin receptor and their *in vivo* efficacy in animal models of cancer*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 169.

OTHER ONCOLYTIC DRUGS

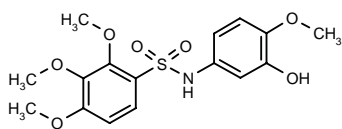
278997

N-(3-Hydroxy-4-methoxyphenyl)-3,4,5-trimethoxybenzenesulfonamide



C16 H19 N O7 S; Mol wt: 369.3921

ACTION – Agent for the treatment of cancer, psoriasis, vascular restenosis, infections, atherosclerosis and hypercholesterolemia that is reported to act through inhibition of abnormal cell proliferation and regulation of LDL receptor expression. *In vitro*, compound exhibited cytotoxicity against human cervical cancer HeLa, human breast cancer MCF-7 and doxorubicin-resistant MCF-7 cells, with IC_{50} values of 0.15, 0.15 and 0.5 μ M, respectively. Another compound from this series of benzenesulfonamides and benzamides is:



278998: C16 H19 N O7 S

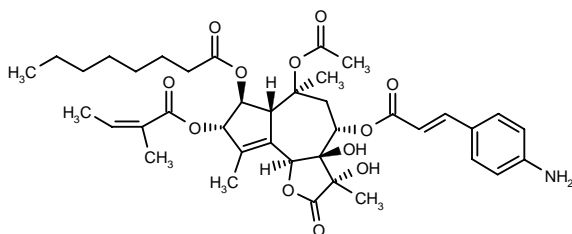
SOURCE – Tularik.

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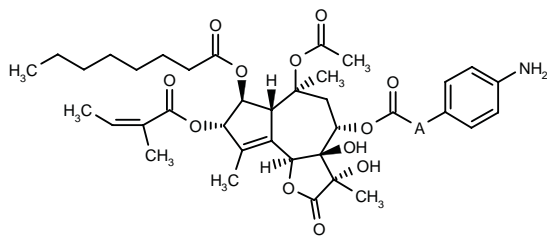
2792861³

2-Methyl-2(*Z*)-butenoic acid (3*S*,3*aR*,4*S*,6*S*,6*aR*,7*S*,8*S*,9*bS*)-6-acetoxy-4-[3-(4-aminophenyl)-2(*E*)-propenoyloxy]-3,3*a*-dihydroxy-7-(octanoyloxy)-2-oxo-3,6,9-trimethyl-2,3,3*a*,4,5,6,6*a*,7,8,9*b*-decahydroazuleno[4,5-*b*]furan-8-yl ester



C39 H51 N O12; Mol wt: 725.8269

ACTION – Antineoplastic agent for the treatment of metastatic prostatic cancer, a thapsigargin analogue containing a primary amine that can be used as an anchoring point for attaching a prostate-specific antigen (PSA)-cleavable peptide. Like thapsigargin, the analogue inhibited endoplasmic reticulum Ca^{2+} -ATPases (SERCA; $\text{IC}_{50} = 18.7 \text{ nM}$), and consequently elevated cytoplasmic Ca^{2+} content by about 6-fold for 4 h at a concentration of $0.30 \text{ }\mu\text{M}$, and it induced apoptosis in human prostate cancer TSU-Pr1 cells ($\text{LC}_{50} = 0.11 \text{ }\mu\text{M}$). Other related compounds are:



Compound	A	Formula
278717 ^{1,2}	-(CH2)2-	C ₃₉ H ₅₃ NO ₁₂
278718 ^{1,2}	-(CH2)3-	C ₄₀ H ₅₅ NO ₁₂

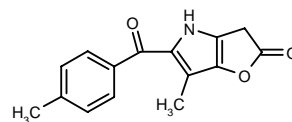
SOURCES – University of Copenhagen, Copenhagen (DK); Johns Hopkins University, Baltimore, MD (US); Royal Danish School of Pharmacy, Copenhagen (DK).

REFERENCES

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- Christensen, S.B. et al. *Thapsigargin analogues for targeting programmed death of androgen-independent prostate cancer cells*. Bioorg Med Chem 1999, 7(7): 1273.
- Procida, K. et al. *ACTA, a fluorescent analogue of thapsigargin, is a potent inhibitor and a conformational probe of skeletal muscle Ca^{2+} -ATPase*. FEBS Lett 1998, 439(1-2): 127.

280241

6-Methyl-5-(4-methylbenzoyl)-3,4-dihydro-2*H*-furo[3,2-*b*]pyrrol-2-one



C15 H13 N O3; Mol wt: 255.2717

ACTION – Antineoplastic agent useful for inducing or promoting apoptosis and arresting uncontrolled neoplastic cell proliferation. Compound potently induces apoptosis in neoplastic cells, but not substantially in normal cells; it also shows no significant inhibition of PGE_2 , and is thus expected to be devoid of the side effects of conventional chemotherapeutics and nonsteroidal antiinflammatory drugs. A representative compound from a series of 1,3,6-trihydro-6-aza-3-oxapentalen-2-one derivatives.

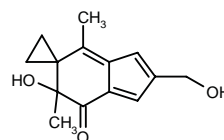
SOURCE – Cell Pathways.

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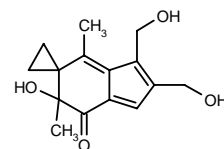
280322

6'-Hydroxy-2'-(hydroxymethyl)-4',6'-dimethyl-6',7'-dihydro-5'*H*-spiro[cyclopropane-1,5'-inden]-7'-one

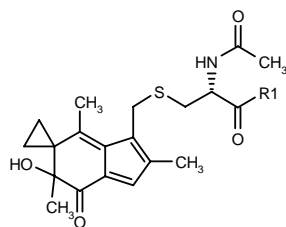


C14 H16 O3; Mol wt: 232.2774

ACTION – Antineoplastic agent with potent cytotoxicity when added to cultures of human lung carcinoma MV522 cells for 48 h ($\text{IC}_{50} = 2640 \text{ nM}$). It was also active *in vivo* in mice bearing MV522 tumors, reducing tumor weight when given at a dose of $14 \text{ mg/kg/day i.p.} \times 5 \text{ days}$. Other representative compounds within this series of illudin analogues include the following:



280323: C15 H18 O4



Compound	R1	Formula
280324	OH	C ₂₀ H ₂₅ NO ₅ S
280325	(R)-NHCH(Me)Ph	C ₂₈ H ₃₄ N ₂ O ₄ S

SOURCE – University of California, Oakland, Oakland, CA (US).

REFERENCES

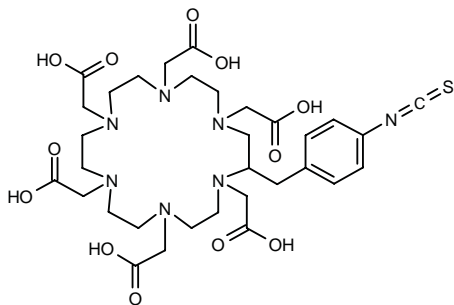
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p-SCN-Bz-HEHA

279591

2-[4,7,10,13,16-Pentakis(carboxymethyl)-2-(4-isothiocyanatobenzyl)-1,4,7,10,13,16-hexaazacyclooctadecan-1-yl]acetic acid

2-(4-Isothiocyanatobenzyl)-1,4,7,10,13,16-hexaazacyclooctadecan-1,4,7,10,13,16-hexakis(acetic acid)



C32 H47 N7 O12 S; Mol wt: 753.8263

ACTION – Bifunctional chelating agent for conjugation with a monoclonal antibody in order to stably complex the α-emitting agent actinium-225 (Ac-225) and therefore suitable for radioimmunotherapy.

SOURCES – National Cancer Institute, Bethesda, MD (US); Oak Ridge National Laboratory, Oak Ridge, TN (US).

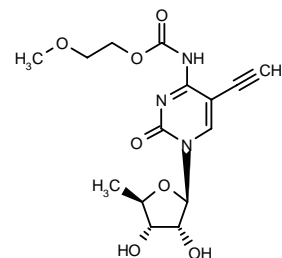
REFERENCES

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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

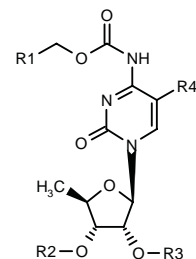
279773

5'-Deoxy-5-ethynyl-*N*⁴-(2-methoxyethoxycarbonyl)cytidine



C15 H19 N3 O7; Mol wt: 353.3291

ACTION – Antineoplastic agent for use in the treatment of malignant diseases alone or in combination with 5-fluorouracil (5-FU) or a derivative thereof; it has been found that the coadministration of compound with 5-FU results in significantly improved selective delivery of 5-FU to tumor tissues as compared with combination of 5-FU and a known dihydropyrimidine dehydrogenase (DPD) inhibitor such as 5-ethynyluracil, and shows significantly improved antitumor activity in human cancer xenograft models. Other specifically claimed compounds from this series of 5'-deoxycytidine derivatives include the following:



Compound	R1	R2=R3	R4	Formula
279774	cyclopentyl	H	ethynyl	C ₁₈ H ₂₃ N ₃ O ₆
279775	3-Pyr	H	ethynyl	C ₁₈ H ₁₈ N ₄ O ₆
279776	CH ₂ C(Me)2OMe	H	vinyl	C ₁₈ H ₂₇ N ₃ O ₇
279777	CH ₂ SMe	H	vinyl	C ₁₅ H ₂₁ N ₃ O ₆ S
279778	CH ₂ C(Me)2OMe	Ac	vinyl	C ₂₂ H ₃₁ N ₃ O ₉
279779	CH ₂ CH ₂ OEt	H	I	C ₁₅ H ₂₂ IN ₃ O ₇
279780	cyclobutyl	H	I	C ₁₅ H ₂₀ IN ₃ O ₆
279781	4-morpholinyl-CH ₂	H	I	C ₁₆ H ₂₃ IN ₄ O ₇

SOURCE – Roche.

REFERENCES

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OCULAR MEDICATIONS

TRAVOPROST

Prop INN

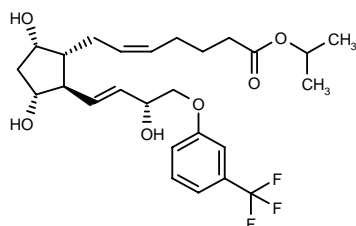
275677

7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

16-[3-(Trifluoromethoxy)phenoxy]-17,18,19,20-tetranor-prostaglandin F_{2α} isopropyl ester

AL-6221

Travatan™



C26 H35 F3 O6; Mol wt: 500.5505

ACTION – Prostaglandin F_{2α} analogue potentially useful for the treatment of glaucoma and ocular hypertension. In rabbits, once-daily topical treatment with compound 0.004% for 1 week induced a significant increase in optic nerve head blood flow, without significant changes in systemic blood pressure or arterial blood gases/pH. The ocular surface hyperemic response following topical application of compound appears to be related with the its ability to induce endothelium-dependent vasodilatation (EC₅₀ = 21 nM in isolated rabbit jugular vein). Phase II clinical studies in patients with open-angle glaucoma and ocular hypertension demonstrated the efficacy and safety of compound as topical therapy for reducing intraocular pressure. Currently undergoing phase III clinical trials.

SOURCE – Alcon.

REFERENCES

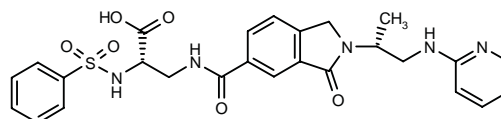
- Klimko, P.G. et al. (Alcon Laboratories, Inc.) *Use of cloprostenol, fluprostenol and their analogues for the manufacture of a medicament for the treatment of glaucoma and ocular hypertension*. EP 639563, JP 95165703, JP 98182465, US 5665773.
- Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 812198, US 5631287, WO 9729752.
- Dean, T.R. et al. *Improvement of optic nerve head blood flow after one-week topical treatment with travoprost (AL-6221) in the rabbit*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2688.
- Garadi, R. et al. *Travoprost: A new once-daily dosed prostaglandin for the reduction of elevated intraocular pressure*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4378.
- Robertson, S. and Silver, L.H. *Dose-response evaluation of travoprost ophthalmic solution (Travatan™), a new topical ocular prostaglandin, in patients with open-angle glaucoma and ocular hypertension*. 12th Congr Eur Soc Ophthalmol (June 27-July 1, Stockholm) 1999, Abst FP153.
- Woodward, D.F. and Chen, J. *Endothelium dependent, nitric oxide (NO) mediated vasorelaxation substantially contributes to ocular surface hyperemic responses produced by prostaglandin F2α (PGF2α) and its analogs*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 912.
- Development status update for antiglaucoma drug candidate*. DailyDrugNews.com (Daily Essentials) 1999, Oct 22.
- Proposed international nonproprietary names (Prop. INN): List 80*. WHO Drug Inf 1998, 12(4): 281.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

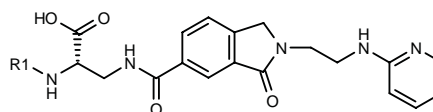
278942

2(*S*)-(Benzenesulfonamido)-3-[2-[1(*R*)-methyl-2-(2-pyridinylamino)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylcarboxamido]propionic acid



C26 H27 N5 O6 S; Mol wt: 537.5943

ACTION – Vitronectin (α_vβ₃) receptor antagonist useful for inhibiting bone resorption and for the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds from this series of isoindolone derivatives include the following:



Compound	R1	Formula
278943	SO ₂ Ph	C ₂₅ H ₂₅ N ₅ O ₆ S
278944	CO ₂ CH ₂ Ph	C ₂₇ H ₂₇ N ₅ O ₆
278945	3-Pyr-SO ₂	C ₂₄ H ₂₄ N ₆ O ₆ S

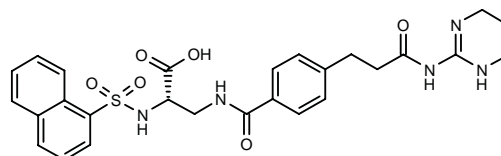
SOURCE – Merck & Co.

REFERENCES

- Duggan, M.E. et al. (Merck & Co., Inc.) *αvβ3 Antagonists*. US 5925655.

279515

2(*S*)-(1-Naphthylsulfonamido)-3-[4-[2-[*N*-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]ethyl]benzamido]propionic acid



C27 H29 N5 O6 S; Mol wt: 551.6211

OCULAR MEDICATIONS

TRAVOPROST

Prop INN

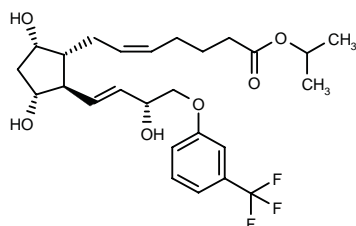
275677

7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[3(*R*)-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1(*E*)-butenyl]cyclopentyl]-5(*Z*)-heptenoic acid isopropyl ester

16-[3-(Trifluoromethoxy)phenoxy]-17,18,19,20-tetranor-prostaglandin F_{2α} isopropyl ester

AL-6221

Travatan™



C26 H35 F3 O6; Mol wt: 500.5505

ACTION – Prostaglandin F_{2α} analogue potentially useful for the treatment of glaucoma and ocular hypertension. In rabbits, once-daily topical treatment with compound 0.004% for 1 week induced a significant increase in optic nerve head blood flow, without significant changes in systemic blood pressure or arterial blood gases/pH. The ocular surface hyperemic response following topical application of compound appears to be related with the its ability to induce endothelium-dependent vasodilatation (EC₅₀ = 21 nM in isolated rabbit jugular vein). Phase II clinical studies in patients with open-angle glaucoma and ocular hypertension demonstrated the efficacy and safety of compound as topical therapy for reducing intraocular pressure. Currently undergoing phase III clinical trials.

SOURCE – Alcon.

REFERENCES

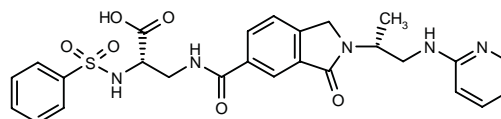
- Klimko, P.G. et al. (Alcon Laboratories, Inc.) *Use of cloprostenol, fluprostenol and their analogues for the manufacture of a medicament for the treatment of glaucoma and ocular hypertension*. EP 639563, JP 95165703, JP 98182465, US 5665773.
- Schneider, L.W. (Alcon Laboratories, Inc.) *Storage-stable prostaglandin compsns*. AU 4649596, EP 812198, US 5631287, WO 9729752.
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- Garadi, R. et al. *Travoprost: A new once-daily dosed prostaglandin for the reduction of elevated intraocular pressure*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4378.
- Robertson, S. and Silver, L.H. *Dose-response evaluation of travoprost ophthalmic solution (Travatan™), a new topical ocular prostaglandin, in patients with open-angle glaucoma and ocular hypertension*. 12th Congr Eur Soc Ophthalmol (June 27-July 1, Stockholm) 1999, Abst FP153.
- Woodward, D.F. and Chen, J. *Endothelium dependent, nitric oxide (NO) mediated vasorelaxation substantially contributes to ocular surface hyperemic responses produced by prostaglandin F2α (PGF2α) and its analogs*. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 912.
- Development status update for antiglaucoma drug candidate*. DailyDrugNews.com (Daily Essentials) 1999, Oct 22.
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

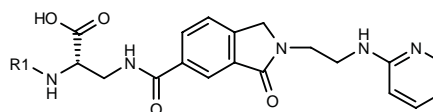
278942

2(*S*)-(Benzenesulfonamido)-3-[2-[1(*R*)-methyl-2-(2-pyridinylamino)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylcarboxamido]propionic acid



C26 H27 N5 O6 S; Mol wt: 537.5943

ACTION – Vitronectin (α_vβ₃) receptor antagonist useful for inhibiting bone resorption and for the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds from this series of isoindolone derivatives include the following:



Compound	R1	Formula
278943	SO ₂ Ph	C ₂₅ H ₂₅ N ₅ O ₆ S
278944	CO ₂ CH ₂ Ph	C ₂₇ H ₂₇ N ₅ O ₆
278945	3-Pyr-SO ₂	C ₂₄ H ₂₄ N ₆ O ₆ S

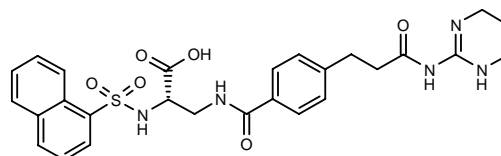
SOURCE – Merck & Co.

REFERENCES

- Duggan, M.E. et al. (Merck & Co., Inc.) *αvβ3 Antagonists*. US 5925655.

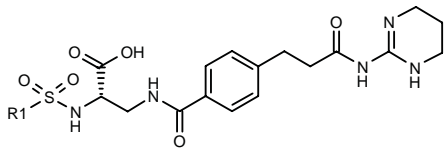
279515

2(*S*)-(1-Naphthylsulfonamido)-3-[4-[2-[*N*-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]ethyl]benzamido]propionic acid



C27 H29 N5 O6 S; Mol wt: 551.6211

ACTION – Integrin $\alpha_v\beta_3$ (vitronectin) receptor antagonist (IC_{50} = 6 nM), potentially useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, inflammation, cardiovascular disorders, restenosis, arteriosclerosis, nephropathies and retinopathies. Other representative compounds within this series of sulfonamide derivatives include the following:



Compound	R1	Formula
279516	2-Naph	C ₂₇ H ₂₉ N ₅ O ₆ S
279517	3-CF ₃ -Ph	C ₂₄ H ₂₆ F ₃ N ₅ O ₆ S
279518	Ph	C ₂₃ H ₂₇ N ₅ O ₆ S
279519	2-thienyl	C ₂₁ H ₂₆ N ₅ O ₆ S ₂
279520	4-CF ₃ -Ph	C ₂₄ H ₂₆ F ₃ N ₅ O ₆ S

SOURCES – Genentech; Hoechst Marion Roussel.

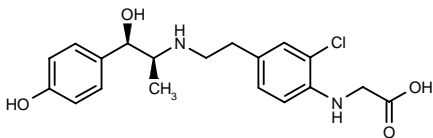
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

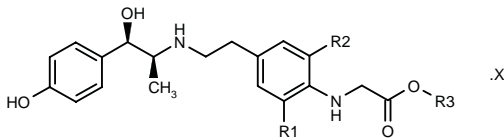
279011

2-[2-Chloro-4-[2-[2(R)-hydroxy-2-(4-hydroxyphenyl)-1(S)-methylethylamino]ethyl]phenylamino]acetic acid



C19 H23 Cl N2 O4; Mol wt: 378.8537

ACTION – Agent for the treatment or prevention of obesity, hyperglycemia, urinary incontinence, depression, cholelithiasis and diseases caused by accelerated intestinal or biliary motion, a potent and selective β_3 -adrenoceptor agonist, as demonstrated in *in vitro* functional studies in ferret urinary bladder smooth muscle (β_3 ; EC_{50} = 0.93 nM), rat atrium (β_1 ; EC_{50} = 23 μ M) and rat uterus (β_2 ; EC_{50} = 3.3 μ M). Other compounds from this series of phenylaminoalkylcarboxylic acid derivatives include the following:



Compound	R1	R2	R3	X	Formula
279012	H	H	H		C ₁₉ H ₂₄ N ₂ O ₄
281430	Cl	Cl	Et	HCl	C ₂₁ H ₂₆ Cl ₂ N ₂ O ₄ .HCl

SOURCE – Kissei.

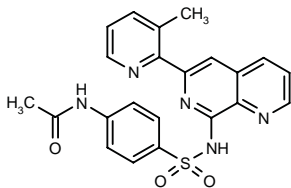
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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

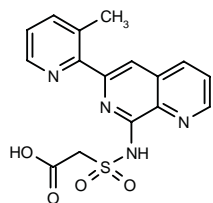
280218

N-[4-[N-[6-(3-Methylpyridin-2-yl)-1,7-naphthyridin-8-yl]-sulfamoyl]phenyl]acetamide



C22 H19 N5 O3 S; Mol wt: 433.4901

ACTION – Granulocyte colony-stimulating factor (G-CSF) production inducer and IL-4 antagonist, potentially useful in the treatment of cancer, allergy, inflammation, autoimmune diseases, certain B-cell lymphomas and for restoring neutrophils after bone marrow transplantation. *In vitro*, it produced a 4-5-fold increase in G-CSF production in phytohemagglutinin (PHA)-stimulated human peripheral blood mononuclear cells (PBMCs) with an EC_{50} value of 15 μ M; no effects on TNF- α , TNF- β , IL-1 α , IL-1 β , IL-3, IL-6, IL-8 or GM-CSF production were observed. An increase in steady-state G-CSF mRNA levels was also observed in cultures of PHA-stimulated PBMCs and lipopolysaccharide-stimulated monocytes. *In vivo*, it was shown to accelerate recovery from neutropenia in cyclophosphamide-treated mice at a dose of 40 mg/kg, being more potent than rhG-CSF at 50-125 mg/kg; G-CSF mRNA levels were shown to be enhanced in this model, thus confirming that compound acts by stimulating endogenous G-CSF production. Another specifically claimed compound from this series of naphthyridine derivatives is:



280219: C16 H14 N4 O4 S

SOURCE – Schering-Plough.

REFERENCES

1. Solomon, D.M. et al. (Schering Corp.) *Naphthyridines which affect IL-4 and G-CSF*. US 5939431.

BLOOD AND BLOOD COMPONENTS

HEXTEND™

238253

Buffered (pH ~ 5.9) artificial colloidal solution containing 6% high-molecular-weight hetastarch (hydroxyethyl starch, mean mol. wt 550 kD) in lactated electrolyte solution (Na⁺, Cl⁻, lactate, Ca²⁺, K⁺, Mg²⁺) and physiological levels of glucose

ACTION – Plasma volume expander.

INDICATION – Treatment of hypovolemia.

PRESENTATION – Single-dose infusion containers for i.v. infusion, 500 ml.

PROPRIETARY NAME – Hextend (US).

SOURCES – BioTime; marketed by Abbott.

REFERENCES

- Abrams, K.J. et al. *Coagulation abnormalities associated with Hextend® a new synthetic colloid solution for isovolemic hemodilution in a canine model*. Anesthesiology 1994, 81(3A, Suppl.): Abst A290.
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16. *BioTime files for Canadian regulatory approval of Hextend*. DailyDrugNews.com (Daily Essentials) 1999, Nov 9.

17. *BioTime lays groundwork for Japanese licensing of Hextend*. DailyDrugNews.com (Daily Essentials) 1998, Jan 20.

18. *BioTime reports preliminary phase III data from Hextend trial*. DailyDrugNews.com (Daily Essentials) 1997, Dec 9.

19. *BioTime to optimize Hextend clinical trial protocol*. BioTime Inc. Press Release 1996, April 2.

20. *FDA approval granted for BioTime's blood plasma volume expander*. DailyDrugNews.com (Daily Essentials) 1999, April 6.

21. *FDA completes review of BioTime's NDA for Hextend*. DailyDrugNews.com (Daily Essentials) 1998, Dec 1.

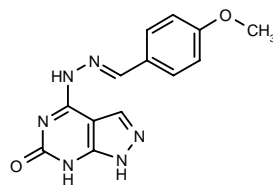
22. *New, physiologically balanced plasma volume expander now available in the U.S.* DailyDrugNews.com (Daily Essentials) 1999, July 15.

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TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

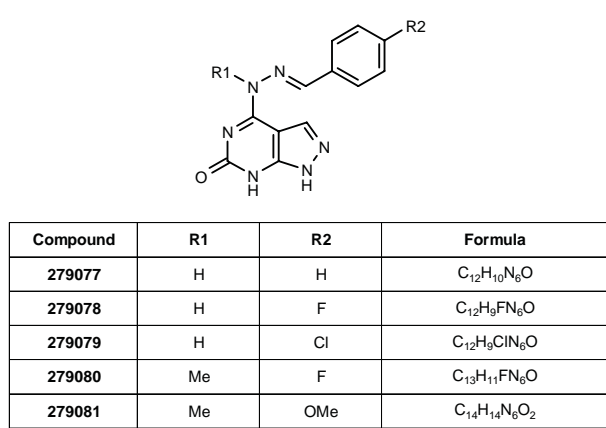
279076

4-Methoxybenzaldehyde *N*-(6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono



C13 H12 N6 O2; Mol wt: 284.2778

ACTION – Uricosuric agent, a xanthine oxidase inhibitor (IC₅₀ = 0.193 μM using bovine milk-derived enzyme), a representative compound from a series of 4-substituted 6-oxo-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives, wherein the following are also included:



SOURCE – Yamasa Shoyu.

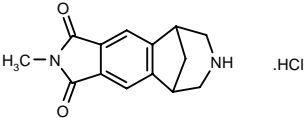
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TREATMENT OF POISONING AND DRUG DEPENDENCY

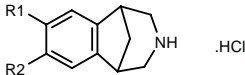
278946

2-Methyl-1,2,3,5,6,7,8,9-octahydro-5,9-methano-pyrrolo[3,4-*h*][3]benzazepine-1,3-dione hydrochloride



C₁₄ H₁₄ N₂ O₂ . HCl; Mol wt: 278.7375

ACTION – Agent for the treatment of nicotine addiction, as well as for other neurological and psychiatric disorders related to reduced cholinergic function such as Huntington’s disease, tardive dyskinesia, schizophrenia, attention deficit hyperactivity disorder, various types of dementia, Parkinson’s disease, anxiety, depression, inflammatory bowel disease, pain and sleep disorders, that acts as an antagonist at neuronal nicotinic acetylcholine receptors. Within this series of aryl-fused azapolycyclic compounds, the following are also included:



Compound	R1	R2	Formula
278947	-N(Me)CON(Me)-		C ₁₄ H ₁₇ N ₃ O.HCl
278948	-CONHCO-		C ₁₃ H ₁₂ N ₂ O ₂ .HCl
278949	F	F	C ₁₁ H ₁₁ F ₂ N.HCl
278950	ethynyl	CN	C ₁₄ H ₁₂ N ₂ .HCl
278951	CF3	Cl	C ₁₂ H ₁₁ ClF ₃ N.HCl
278952	CF3	CN	C ₁₃ H ₁₁ F ₃ N ₂ .HCl

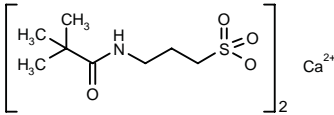
SOURCE – Pfizer.

REFERENCES

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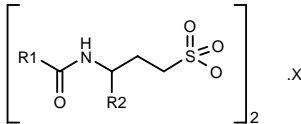
279337

Calcium di(3-pivalamidopropane-1-sulfonate)



2 C₈ H₁₆ Ca N O₄ S; Mol wt: 484.6448

ACTION – Agent for the treatment of alcohol dependence shown to decrease ethanol consumption in alcohol-dependent rats at 100 mg/kg/day i.p. x 2 weeks. *In vitro*, it was shown to displace [³H]-calcium acetylhomotaurinate from rat brain preparations with an IC₅₀ value of 46.9 μM. Other compounds from this series of sulfonic, phosphonic and phosphinic aminoalkane acid derivatives include the following:



Compound	R1	R2	X	Formula
279338	i-Pr	H	Mg2+	C ₁₄ H ₂₈ MgN ₂ O ₈ S ₂
279339	i-Bu	H	Mg2+	C ₁₆ H ₃₂ MgN ₂ O ₈ S ₂
279340	t-Bu	H	Mg2+	C ₁₆ H ₃₂ MgN ₂ O ₈ S ₂
279341	Me	Me	Ca2+	C ₁₂ H ₂₄ CaN ₂ O ₈ S ₂

SOURCE – Lipha.

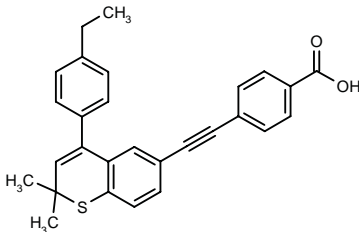
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AGN-194310

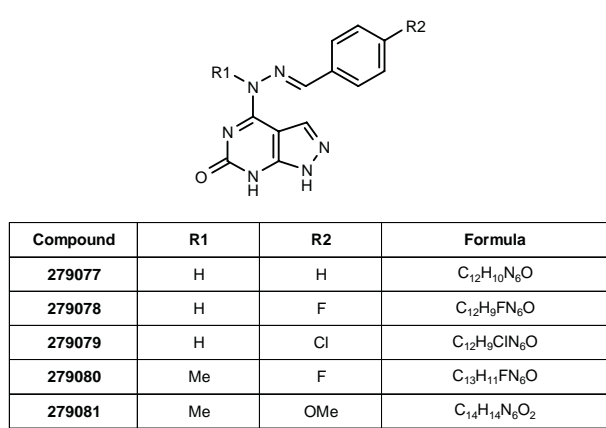
275399

4-[2-[4-(4-Ethylphenyl)-2,2-dimethyl-2H-1-benzothio-pyran-6-yl]ethynyl]benzoic acid



C₂₈ H₂₄ O₂ S; Mol wt: 424.5616

ACTION – Retinoid A receptor (RAR) antagonist with high affinity for all three RAR subtypes (K_d = 3, 2 and 5 nM, respectively, for RARα, RARβ and RARγ receptors). In functional studies, compound showed antagonist activity *in vitro* and *in vivo*, as demonstrated by inhibition of the transcriptional activity of TTNPB and inhibition of the topical toxicity induced by TTNPB. Potentially useful for the treatment of the mucocutaneous toxicity produced by systemic retinoids, as well as for the treatment of diseases involving RAR activation.



SOURCE – Yamasa Shoyu.

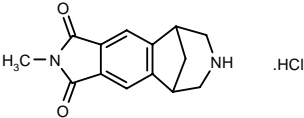
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TREATMENT OF POISONING AND DRUG DEPENDENCY

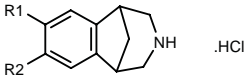
278946

2-Methyl-1,2,3,5,6,7,8,9-octahydro-5,9-methano-pyrrolo[3,4-*h*][3]benzazepine-1,3-dione hydrochloride



C₁₄ H₁₄ N₂ O₂ . HCl; Mol wt: 278.7375

ACTION – Agent for the treatment of nicotine addiction, as well as for other neurological and psychiatric disorders related to reduced cholinergic function such as Huntington’s disease, tardive dyskinesia, schizophrenia, attention deficit hyperactivity disorder, various types of dementia, Parkinson’s disease, anxiety, depression, inflammatory bowel disease, pain and sleep disorders, that acts as an antagonist at neuronal nicotinic acetylcholine receptors. Within this series of aryl-fused azapolycyclic compounds, the following are also included:



Compound	R1	R2	Formula
278947	-N(Me)CON(Me)-		C ₁₄ H ₁₇ N ₃ O.HCl
278948	-CONHCO-		C ₁₃ H ₁₂ N ₂ O ₂ .HCl
278949	F	F	C ₁₁ H ₁₁ F ₂ N.HCl
278950	ethynyl	CN	C ₁₄ H ₁₂ N ₂ .HCl
278951	CF3	Cl	C ₁₂ H ₁₁ ClF ₃ N.HCl
278952	CF3	CN	C ₁₃ H ₁₁ F ₃ N ₂ .HCl

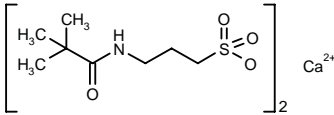
SOURCE – Pfizer.

REFERENCES

1. Coe, J.W. and Brooks, P.R.P. (Pfizer Products Inc.) Aryl fused azapolycyclic cpds. WO 9935131.

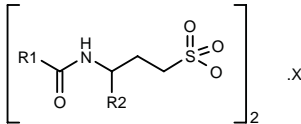
279337

Calcium di(3-pivalamidopropane-1-sulfonate)



2 C₈ H₁₆ Ca N O₄ S; Mol wt: 484.6448

ACTION – Agent for the treatment of alcohol dependence shown to decrease ethanol consumption in alcohol-dependent rats at 100 mg/kg/day i.p. x 2 weeks. *In vitro*, it was shown to displace [³H]-calcium acetylhomotaurinate from rat brain preparations with an IC₅₀ value of 46.9 μM. Other compounds from this series of sulfonic, phosphonic and phosphinic aminoalkane acid derivatives include the following:



Compound	R1	R2	X	Formula
279338	i-Pr	H	Mg2+	C ₁₄ H ₂₈ MgN ₂ O ₈ S ₂
279339	i-Bu	H	Mg2+	C ₁₆ H ₃₂ MgN ₂ O ₈ S ₂
279340	t-Bu	H	Mg2+	C ₁₆ H ₃₂ MgN ₂ O ₈ S ₂
279341	Me	Me	Ca2+	C ₁₂ H ₂₄ CaN ₂ O ₈ S ₂

SOURCE – Lipha.

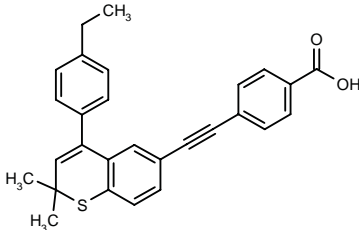
REFERENCES

1. Berthelon, J.-J. and Durbin, P. (Lipha Santé) New derivs. of sulfonic, phosphonic and phosphinic aminoalkane acids, their production and their use as medicaments. WO 9937606.

AGN-194310

275399

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C₂₈ H₂₄ O₂ S; Mol wt: 424.5616

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SOURCE – Allergan.

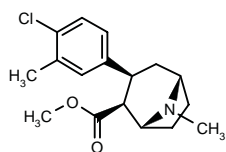
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3. Allergan: *Annual Report 1998/Q1 1999*. DailyDrugNews.com (Daily Essentials) 1999, May 5.

RTI-112

279525

(-)-(1*R*,2*S*,3*S*,5*S*)-(4-Chloro-3-methylphenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester



C17 H22 Cl N O2; Mol wt: 307.8188

M.p. 186-7 °C; $[\alpha]_D^{23}$ -89.5° (*c* 0.095, MeOH).

ACTION – Cocaine analogue with high affinity for the dopamine transporter (IC_{50} = 0.81 nM for displacement of [³H]-Win-35428 binding in rat striatal membranes) with moderate to high selectivity over norepinephrine and 5-HT transporters (K_i = 36.2 and 10.5 nM, respectively); it showed 100-fold higher affinity for the dopamine transporter than cocaine (IC_{50} = 89 nM). *In vivo*, it exhibited comparable potency to cocaine in antagonizing nicotine-induced antinociceptive effects in mice (tail-flick test; AD_{50} = 3.5 and 3.2 μmol/kg s.c. for compound and cocaine, respectively) and it was more potent than cocaine in antagonizing nicotine-induced hypothermia in mice (AD_{50} = 1.5 μmol/kg s.c.). Potentially useful as a nicotine antagonist in smoking cessation, and also in the development of cocaine antagonists.

SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

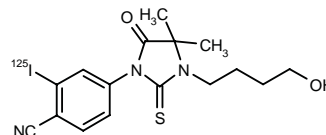
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1. Carroll, F.I. *Development of 3-phenyltropane analogs as medications for treating cocaine abuse*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 158.
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4. Damaj, M.I. et al. *Pharmacological characterization of nicotine's interaction with cocaine and cocaine analogs*. J Pharmacol Exp Ther 1999, 289(3): 1229.
5. Ivy Carroll, F. et al. *Cocaine and 3β-(4'-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogues. New high-affinity and selective compounds for the dopamine transporter*. J Med Chem 1995, 38(2): 379.
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DIAGNOSTIC AGENTS

279625

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-([¹²⁵I]-iodo)benzonitrile



C16 H18 I N3 O2 S; Mol wt: 441.4032

ACTION – High-affinity and selective androgen receptor ligand (K_a = 6.1 nM for rat prostate receptor) that, in iodinated form, may represent a potential clinically useful radioligand for single photon emission computed tomography (SPECT) imaging of tumor sites in prostate cancer.

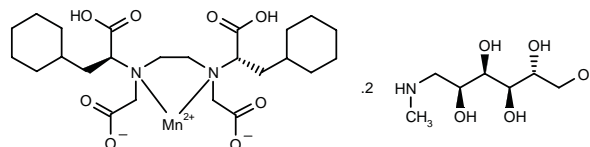
SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

1. Van Dort, M.E. et al. *Development of a radioiodinated nonsteroidal ligand for the androgen receptor*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 220.

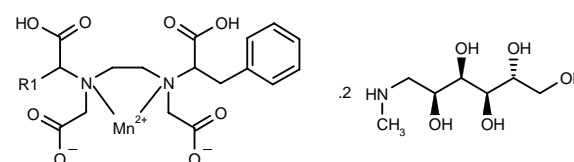
281277

Dihydrogen [[*N,N'*-(1,2-ethanediyl)bis[*N*-(carboxymethyl)-3-cyclohexyl-L-alaninato]](4-)]manganate(2-) compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)



C24 H38 N2 O8 . 2 C7 H17 N O5 . Mn; Mol wt: 927.9348

ACTION – Manganese chelate with high relaxivity in serum, considered to be particularly useful for magnetic resonance imaging (MRI) of the liver, pancreas and gastrointestinal tract. Other exemplified compounds include the following:



Compound	R1	Isomer	Formula
281278	H	R	C ₃₁ H ₅₄ MnN ₄ O ₁₈
281279	CH2Ph	S,S	C ₃₈ H ₆₀ MnN ₄ O ₁₈

SOURCE – Allergan.

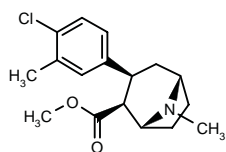
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RTI-112

279525

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M.p. 186-7 °C; $[\alpha]_D^{23}$ –89.5° (*c* 0.095, MeOH).

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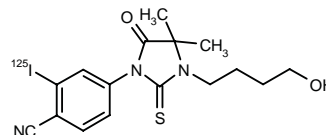
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279625

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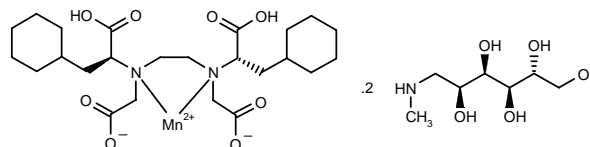
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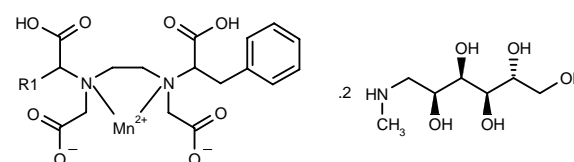
281277

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C24 H38 N2 O8 . 2 C7 H17 N O5 . Mn; Mol wt: 927.9348

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SOURCES – Bracco; Dibra.

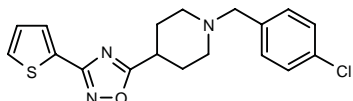
REFERENCES

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PHARMACOLOGICAL TOOLS

279799

1-(4-Chlorobenzyl)-4-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]piperidine



C18 H18 Cl N3 O S; Mol wt: 359.8792

ACTION – Potent and selective dopamine D₄ receptor ligand with K_i values of 5 and 850 nM for human dopamine D₄ and D₂ receptors, respectively.

SOURCE – CombiChem.

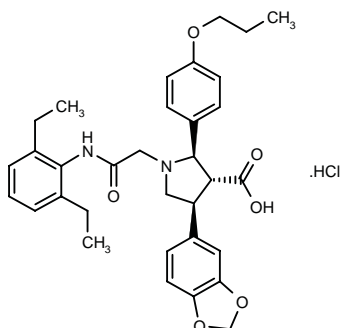
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A-192621*

255885

(2*R*,3*R*,4*S*)-4-(1,3-Benzodioxol-5-yl)-1-[*N*-(2,6-diethylphenyl)carbamoylmethyl]-2-(4-propoxyphenyl)pyrrolidine-3-carboxylic acid hydrochloride



C33 H38 N2 O6 . HCl; Mol wt: 595.1321

ACTION – Potent and selective endothelin ET_B antagonist (IC₅₀ = 6.4 nM) with 1300-fold selectivity over ET_A receptors (IC₅₀ = 8200 nM) and *in vitro* functional antagonist activity against ET-mediated inositol phosphate hydrolysis (IC₅₀ = 0.65 nM). In anesthetized rats, a dose of 30 mg/kg p.o. completely blocked the ET-1-induced transient depressor effect, while having no effect on the pressor response. Chronic dosing with compound in rats (10-100 mg/kg/day in the food for 7 days) and cynomolgus monkeys (1-10 mg/kg b.i.d. for 4 days) produced dose-

dependent increases in blood pressure mediated through activation of ET_A receptors. Potentially useful as a pharmacological tool to elucidate the role of the ET_B receptor in the regulation of arterial pressure.

SOURCE – Abbott.

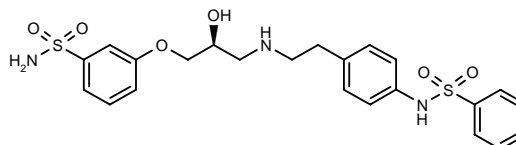
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 6. Hashimoto, M.Y. et al. *Different contribution of endothelin-A and endothelin-B receptors in the pathogenesis of deoxycorticosterone acetate-salt-induced hypertension in rats*. Hypertension 1999, 33(2): 759.
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 8. Matsumura, Y. et al. *Roles of ET_A and ET_B receptors in the pathogenesis of DOCA-salt-induced hypertension in rats*. Jpn J Pharmacol 1999, 79(Suppl. 1): Abst O-195.
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- *Identified compound **255885** (see **255043**) Drug Data Rep 1997, 019(11): 0986.

L-748328

279348

3-[2(*S*)-Hydroxy-3-[2-[4-(phenylsulfonamido)phenyl]-ethylamino]propoxy]benzenesulfonamide



C23 H27 N3 O6 S2; Mol wt: 505.6133

SOURCES – Bracco; Dibra.

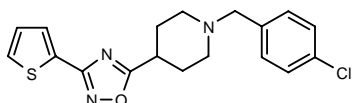
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PHARMACOLOGICAL TOOLS

279799

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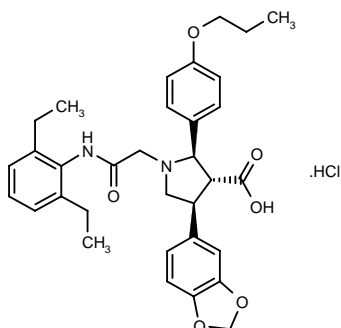
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SOURCE – Abbott.

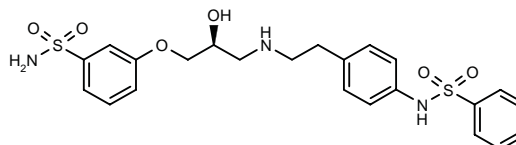
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 9. Mills, T.M. et al. *Influence of endothelin-1 on the rat erectile response: Role of ET_A and ET_B receptors*. Int J Impot Res 1999, 11(Suppl. 1): Abst B12.
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L-748328

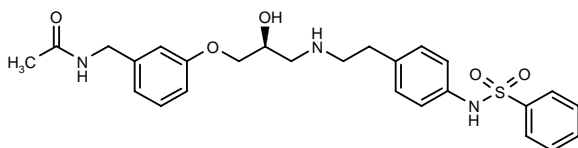
279348

3-[2(*S*)-Hydroxy-3-[2-[4-(phenylsulfonamido)phenyl]-ethylamino]propoxy]benzenesulfonamide



C23 H27 N3 O6 S2; Mol wt: 505.6133

ACTION – Potent and selective β_3 -adrenoceptor (AR) antagonist with nanomolar affinity for human β_3 -adrenoceptors ($K_i = 3.7$ nM) and more than 90- and 20-fold selectivity over β_1 - and β_2 -AR ($K_i = 467$ and 99 nM, respectively). Compound also showed high affinity and selectivity for rhesus monkey β_3 -AR ($K_i = 5.1$, 653 and 97 nM for β_3 -, β_1 - and β_2 -AR, respectively, expressed in CHO cells). Competitive β_3 -AR-antagonist properties were demonstrated by its ability to inhibit the isoproterenol-induced increase in cAMP production in CHO cells expressing β_3 -AR ($IC_{50} = 4.6$ nM; $pA_2 = 8.5$). L-748328 inhibited the lipolytic response elicited by the β_3 -selective agonist L-742791 in rhesus monkey adipose tissue with an IC_{50} of 13 nM. A potential pharmacological tool for *in vitro* studies on β_3 -AR. Another related compound is:



L-748337 [279349]: C₂₆ H₃₁ N₃ O₅ S

SOURCE – Merck & Co.

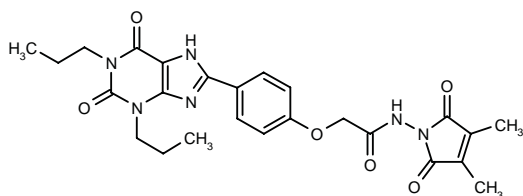
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MRS-1595

279526

N-(3,4-Dimethyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-[4-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)phenoxy]acetamide



C₂₅ H₂₈ N₆ O₆; Mol wt: 508.5322

ACTION – Potent and selective adenosine A_{2B} receptor antagonist ($K_i = 1.48$ nM in HEK-293 cells expressing human receptor) with 27- and 17-fold selectivity over human A_1 and A_{2A} receptors, respectively, and 300-fold selectivity over other adenosine receptor subtypes. Potentially useful as a pharmacological tool for elucidating the physiological role of the adenosine A_{2B} receptor.

SOURCES – National Institutes of Health, Bethesda, MD (US); University of Virginia, Charlottesville, VA (US).

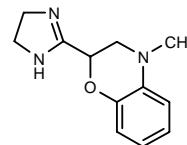
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S-22954

279621

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine



C₁₂ H₁₅ N₃ O; Mol wt: 217.2705

ACTION – Potent and rapid-acting hyperglycemic agent able to significantly increase blood glucose levels in both fed and fasted mice at a dose of 25 mg/kg i.p. Compound was more potent than the reference hyperglycemic agent diazoxide. This imidazoline compound was seen to enhance K_{ATP} channel activation in rat isolated aortic rings.

SOURCE – Servier.

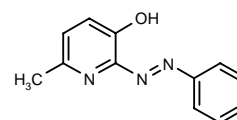
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SIB-1757^{1-4,6}

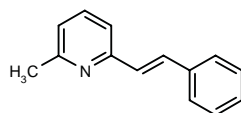
274597

6-Methyl-2-[(*E*)-2-phenyldiazenyl]-3-pyridinol



C₁₂ H₁₁ N₃ O; Mol wt: 213.2389

ACTION – Noncompetitive metabotropic glutamate subtype 5a (mglu5a) receptor antagonist ($IC_{50} = 0.37$ μ M against recombinant human receptor) with little or no agonist or antagonist activity at other recombinant human mglu receptor subtypes, AMPA, kainate or NMDA receptor subtypes (EC_{50} or $IC_{50} > 30$ μ M). Compound inhibited DHPG-induced inositol phosphate accumulation in hippocampus and striatum of neonatal rat brain preparations with IC_{50} values of 5.2 and 10.1 μ M, respectively, as well as DHPG-evoked intracellular calcium increase in cultured cortical neurons (88% inhibition at 10 μ M). Potentially useful as a pharmacological tool to evaluate the role of this receptor in normal physiology and in neurodegenerative disorders, pain and epilepsy. Another related compound is:



SIB-1893 [274598]¹⁻⁶: C₁₄ H₁₃ N

SOURCES – Novartis; Sibia Neurosciences.

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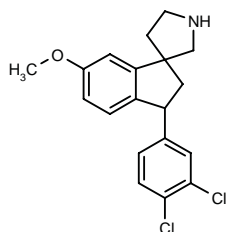
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ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

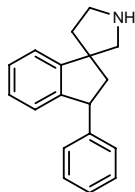
280445

3-(3,4-Dichlorophenyl)-6-methoxyspiro[indan-1,3'-pyrrolidine]



C₁₉ H₁₉ Cl₂ N O; Mol wt: 348.2711

ACTION – Monoamine reuptake inhibitor, particularly 5-HT reuptake inhibitor, with potential in the treatment of pain, headache, migraine, depression, obesity, sexual dysfunction, alcoholism, bulimia, anorexia, attention deficit hyperactivity disorder, obsessive-compulsive disorder and impulse control disorder. Compound exhibited high affinity and selectivity for the high-affinity cocaine binding site on the 5-HT transporter (SERT-1; IC₅₀ = 0.002 μM) as compared to the paroxetine binding site on the 5-HT transporter (SERT-2; IC₅₀ = 0.4 μM) and the dopamine transporter (DAT; IC₅₀ = 0.15 μM), while showing very weak affinity for μ- and κ-opioid receptors (IC₅₀ = 5 and 80 μM, respectively). Another specifically claimed compound from this series of spiroindanamines and spiroindan-amides is:



280446: C₁₈ H₁₉ N

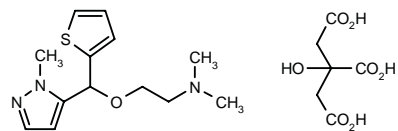
SOURCE – University of Minnesota, Minneapolis, MN (US).

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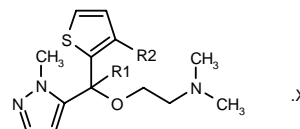
281884

(-)-*N,N*-Dimethyl-*N*-[2-[1-(1-methyl-1*H*-pyrazol-5-yl)-1-(2-thienyl)methoxy]ethyl]amine citrate



C₁₃ H₁₉ N₃ O S . C₆ H₈ O₇; Mol wt: 457.5013

ACTION – Analgesic agent found to be active in the phenylbenzoquinone-induced writhing test in mice, producing 87% inhibition at a dose of 160 mg/kg p.o. Other representative compounds from a series of thienylazolyalkoxyethanamines include the following:



Compound	R1	R2	Isomer	X	Formula
281885	H	H			C ₁₃ H ₁₉ N ₃ OS
281886	H	H		citrate	C ₁₃ H ₁₉ N ₃ OS.C ₆ H ₈ O ₇
281887	H	Me			C ₁₄ H ₂₁ N ₃ OS
281888	Me	H			C ₁₄ H ₂₁ N ₃ OS
281889	H	H	(+)	citrate	C ₁₃ H ₁₉ N ₃ OS.C ₆ H ₈ O ₇

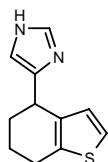
SOURCE – Esteve.

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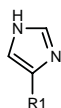
281916

4-(4,5,6,7-Tetrahydrobenzo[*b*]thien-4-yl)-1*H*-imidazole



C₁₁ H₁₂ N₂ S; Mol wt: 204.2958

ACTION – Analgesic agent with α_{2D} -adrenoceptor-agonist activity ($K_i = 0.56$ nM against [³H]-*p*-aminoclonidine binding in rat cortex membranes). Antinociceptive activity was demonstrated in the mouse acetylcholine bromide-induced abdominal constriction assay (100% inhibition at 30 mg/kg p.o.). A representative compound from a series of 4-(benzothienyl)imidazole derivatives, wherein the following are also included:



Compound	R1	Formula
281917	4-benzothienyl	C ₁₁ H ₈ N ₂ S
281920	1,3-(Me)2-6,7-dihydro-4-isobenzothienyl	C ₁₃ H ₁₄ N ₂ S
281921	1,3-(Me)2-4,5,6,7-tetrahydro-4-isobenzothienyl	C ₁₃ H ₁₆ N ₂ S
281922	4,5,6,7-tetrahydro-7-benzothienyl	C ₁₁ H ₁₂ N ₂ S
281923	4,5-dihydro-7-benzothienyl	C ₁₁ H ₁₀ N ₂ S

SOURCE – Ortho-McNeil.

REFERENCES

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C0401

280439

Injectable, sustained-release formulation of DepoFoam™-encapsulated morphine sulfate

D0401
DepoMorphine™

ACTION – Injectable, sustained-release formulation of DepoFoam™-encapsulated morphine for the treatment of acute postoperative pain. Preliminary data from an ongoing open-label clinical phase II trial showed that a single epidural injection of compound is markedly superior to a single dose of intrathecal or epidural morphine in terms of duration and quality of analgesia; the side effect profile is similar to standard opioid therapy.

SOURCE – DepoTech.

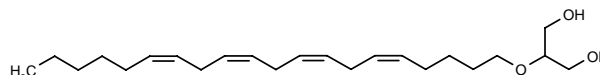
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HU-310

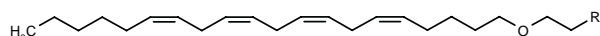
281861

2-[Icosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenyloxy]propane-1,3-diol



C₂₃ H₄₀ O₃; Mol wt: 364.5660

ACTION – Endogenous cannabinoid analogue that binds to cannabinoid CB₁ and CB₂ receptors for a prolonged period of time and exhibits *in vivo* effects similar to those of anandamide and 2-arachidonyl glycerol, i.e., analgesic, antiemetic, antiglaucoma, hypotensive, antiinflammatory and antispastic effects. It gave an ED₅₀ value in the hot-plate assay in mice of 2.8 mg/kg i.v.; it reduced cisplatin-induced vomiting in pigeons by 50% at a dose of 3.0 mg/kg s.c.; it reduced intraocular pressure (IOP) in rabbits with chymotrypsin-induced glaucoma at a concentration of 0.1%; it inhibited arachidonic acid-induced paw edema in mice by 100% at a dose of 25 mg/kg s.c.; and it produced significant and long-lasting decreases in blood pressure in rats at a dose of 12 mg/kg i.v. Other exemplified compounds include the following:



Compound	R1	Formula
HU-313 [281862]	i-PrO	C ₂₅ H ₄₄ O ₂
HU-314 [281863]	Me	C ₂₃ H ₄₀ O

SOURCE – Yissum.

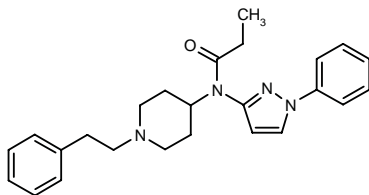
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NJA-92

280432

N-[1-(2-Phenylethyl)piperidin-4-yl]-*N*-(1-phenyl-1*H*-pyrazol-3-yl)propionamide



C₂₅ H₃₀ N₄ O; Mol wt: 402.5390

ACTION – Opioid analgesic able to induce concentration-dependent inhibition (60% at 0.2-0.8 μ M) of electrically induced contractions in isolated guinea pig ileum myenteric plexus-longitudinal muscle strip preparations, an effect which was reversed by naloxone. *In vivo*, compound showed analgesic activity in two models of hyperalgesia in mice: the abdominal constriction test, where it was effective at 0.05 and 0.5 mg/kg i.p., and the hot-plate test, effects which were also reversed by naloxone.

SOURCES – Universidad Complutense de Madrid, Madrid (ES); CSIC, Madrid (ES).

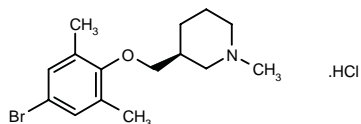
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RS-132943

280431

3(*S*)-(4-Bromo-2,6-dimethylphenoxy)methyl)-1-methylpiperidine hydrochloride



C₁₅ H₂₂ Br N O . HCl; Mol wt: 348.7097

ACTION – Analgesic agent, a sodium channel blocker able to produce dose-dependent and long-lasting (3-5 h) reversal of mechanical allodynia in spinal nerve-ligated rats (ED₅₀ = 377 mg/kg p.o.), as well as to inhibit heat hyperalgesia and cold allodynia in rats with chronic constriction injury (ED₅₀ = 16 and 55 mg/kg p.o., respectively). When administered chronically for 5 days at doses inactive when administered acutely (10 and 20 mg/kg p.o.), it was able to produce a reversal of cold allodynia. Compound at doses up to 600 mg/kg p.o. did not induce behavioral effects in rats. Potentially useful for the treatment of neuropathic pain.

SOURCE – Roche Bioscience.

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ANTIMIGRAINE DRUGS

LOMERIZINE HYDROCHLORIDE

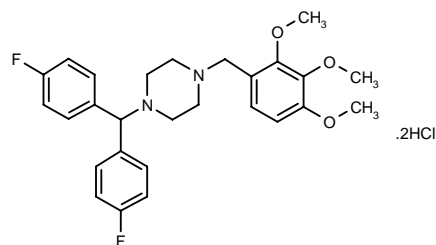
Rec INNM

130942

115408 (as free base)

1-[Bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride

KB-2796⁺



C₂₇ H₃₀ F₂ N₂ O₃ . 2HCl; Mol wt: 541.4628

ACTION – Antimigraine agent, a calcium channel blocker with the ability to inhibit vasoconstriction caused by intracellular influx of calcium ions.

INDICATION – Prophylaxis of migraine.

PRESENTATION – Tablets, 5 mg.

PROPRIETARY NAME – Terranas (JP).

SOURCES – Nippon Organon; codeveloped by Pharmacia & Upjohn and Kanebo (now Nippon Organon).

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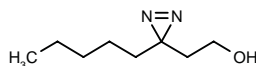
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+Drug Data Rep 1987, 009(06): 0509.

ANESTHETIC DRUGS

279999

2-(3-Pentyl-3H-1,2-diaziren-3-yl)ethanol



C₈ H₁₆ N₂ O; Mol wt: 156.2274

ACTION – Reversible general anesthetic proven to induce anesthesia in tadpoles with an ED_{50} of 160 μM and a potency between that of heptanol and octanol. At subanesthetic concentrations, compound was seen to enhance both GABA-induced currents and [^3H]-muscimol binding to GABA_A receptors. In the muscle-subtype nicotinic acetylcholine receptors (nAChR), compound inhibited the ACh response with an IC_{50} of 33 μM . When activated by nondamaging UV wavelengths, the compound photoincorporated into nAChR-rich membranes, mainly in the α subunit and particularly in the desensitized state, suggesting that it interacts with a novel binding site.

SOURCES – Harvard Medical School, Boston, MA (US); Massachusetts General Hospital, Boston, MA (US); UCLA School of Medicine, Los Angeles, CA (US).

REFERENCES

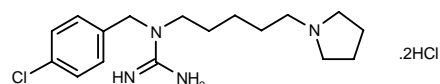
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

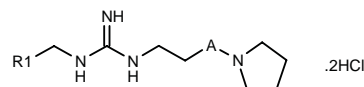
280385

N-(4-Chlorobenzyl)-N-[5-(1-pyrrolidiny)pentyl]guanidine dihydrochloride

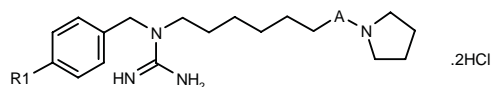


C₁₇ H₂₇ Cl N₄ . 2HCl; Mol wt: 395.8031

ACTION – Histamine H₃ receptor ligand, as demonstrated in binding and functional studies by a pK_i value of 9.0 for inhibition of [^3H]-(*R*)- α -methylhistamine binding in guinea pig cortex preparations, and a pK_B value of 7.9 for inhibition of electrically stimulated contractions in guinea pig ileal longitudinal muscle strips. Potentially useful as a sedative, sleep regulator, anticonvulsant, regulator of hypothalamo-hypophyseal secretion, antidepressant, modulator of cerebral circulation, and for the treatment of asthma and irritable bowel syndrome. Other exemplified compounds include the following:



Compound	R1	A	Formula
280386	4-Cl-PhCH ₂	-CH ₂ -	C ₁₆ H ₂₅ ClN ₄ .2HCl
280387	1-adamantyl	-(CH ₂) ₂ -	C ₂₀ H ₃₆ N ₄ .2HCl
280388	1-adamantyl	-(CH ₂) ₃ -	C ₂₁ H ₃₈ N ₄ .2HCl
280389	1-adamantyl	-(CH ₂) ₄ -	C ₂₂ H ₄₀ N ₄ .2HCl
280390	1-adamantyl	-(CH ₂) ₅ -	C ₂₃ H ₄₂ N ₄ .2HCl
280391	cyclohexyl	-(CH ₂) ₃ -	C ₁₇ H ₃₄ N ₄ .2HCl



Compound	R1	A	Formula
280392	Cl	-CH ₂ -	C ₁₉ H ₃₁ ClN ₄ .2HCl
280393	H	bond	C ₁₈ H ₃₀ N ₄ .2HCl

SOURCE – James Black Foundation.

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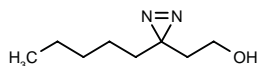
MONOGRAPH – Prous, J. and Castañer, J. *KB-2796.* Drugs Fut 1988, 13(4): 0312.

+Drug Data Rep 1987, 009(06): 0509.

ANESTHETIC DRUGS

279999

2-(3-Pentyl-3*H*-1,2-diaziren-3-yl)ethanol



C₈ H₁₆ N₂ O; Mol wt: 156.2274

ACTION – Reversible general anesthetic proven to induce anesthesia in tadpoles with an ED₅₀ of 160 μM and a potency between that of heptanol and octanol. At subanesthetic concentrations, compound was seen to enhance both GABA-induced currents and [³H]-muscimol binding to GABA_A receptors. In the muscle-subtype nicotinic acetylcholine receptors (nAChR), compound inhibited the ACh response with an IC₅₀ of 33 μM. When activated by nondamaging UV wavelengths, the compound photoincorporated into nAChR-rich membranes, mainly in the α subunit and particularly in the desensitized state, suggesting that it interacts with a novel binding site.

SOURCES – Harvard Medical School, Boston, MA (US); Massachusetts General Hospital, Boston, MA (US); UCLA School of Medicine, Los Angeles, CA (US).

REFERENCES

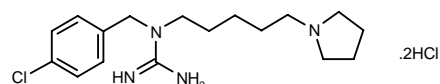
1. Husain, S.S. et al. *Synthesis and properties of 3-(2-hydroxyethyl)-3-N-pentyl-diazirine, a photoactivable general anesthetic.* J Med Chem 1999, 42(17): 3300.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

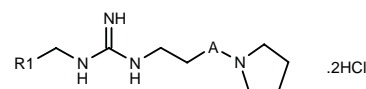
280385

N-(4-Chlorobenzyl)-*N*-[5-(1-pyrrolidiny)pentyl]guanidine dihydrochloride

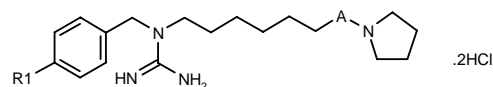


C₁₇ H₂₇ Cl N₄ . 2HCl; Mol wt: 395.8031

ACTION – Histamine H₃ receptor ligand, as demonstrated in binding and functional studies by a pK_i value of 9.0 for inhibition of [³H]-(*R*)-α-methylhistamine binding in guinea pig cortex preparations, and a pK_B value of 7.9 for inhibition of electrically stimulated contractions in guinea pig ileal longitudinal muscle strips. Potentially useful as a sedative, sleep regulator, anticonvulsant, regulator of hypothalamo-hypophyseal secretion, antidepressant, modulator of cerebral circulation, and for the treatment of asthma and irritable bowel syndrome. Other exemplified compounds include the following:



Compound	R1	A	Formula
280386	4-Cl-PhCH ₂	-CH ₂ -	C ₁₆ H ₂₅ ClN ₄ .2HCl
280387	1-adamantyl	-(CH ₂) ₂ -	C ₂₀ H ₃₆ N ₄ .2HCl
280388	1-adamantyl	-(CH ₂) ₃ -	C ₂₁ H ₃₈ N ₄ .2HCl
280389	1-adamantyl	-(CH ₂) ₄ -	C ₂₂ H ₄₀ N ₄ .2HCl
280390	1-adamantyl	-(CH ₂) ₅ -	C ₂₃ H ₄₂ N ₄ .2HCl
280391	cyclohexyl	-(CH ₂) ₃ -	C ₁₇ H ₃₄ N ₄ .2HCl



Compound	R1	A	Formula
280392	Cl	-CH ₂ -	C ₁₉ H ₃₁ ClN ₄ .2HCl
280393	H	bond	C ₁₈ H ₃₀ N ₄ .2HCl

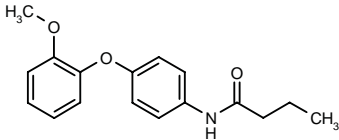
SOURCE – James Black Foundation.

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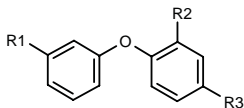
281358

N-[4-(2-Methoxyphenoxy)phenyl]butyramide



C17 H19 N O3; Mol wt: 285.3411

ACTION – Agent for the treatment of sleep and chronobiological disorders that acts by virtue of its melatonergic activity. A representative compound from a series of aryloxyanilide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
281359	OMe	H	NHCOPr	C ₁₇ H ₁₉ NO ₃
281360	OMe	NHCOPr	H	C ₁₇ H ₁₉ NO ₃
281361	OMe	i-PrCONH	H	C ₁₇ H ₁₉ NO ₃
281362	OMe	H	NHAc	C ₁₅ H ₁₅ NO ₃
281363	OMe	H	NHCOEt	C ₁₆ H ₁₇ NO ₃
281364	OMe	H	NHCOCH ₂ OMe	C ₁₆ H ₁₇ NO ₄
281365	OMe	H	i-PrCONH	C ₁₇ H ₁₉ NO ₃
281366	CO ₂ Me	H	NHCOPr	C ₁₈ H ₁₉ NO ₄
281367	CO ₂ Me	H	cyclopropyl-CONH	C ₁₈ H ₁₇ NO ₄
281368	F	H	NHCOPr	C ₁₆ H ₁₆ FNO ₂
281369	OMe	H	cyclopropyl-CONH	C ₁₇ H ₁₇ NO ₃
281370	OMe	H	vinyl-CONH	C ₁₆ H ₁₅ NO ₃

SOURCE – Bristol-Myers Squibb.

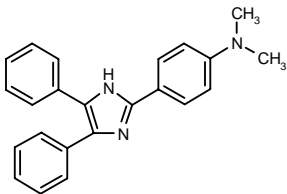
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ANXIOLYTICS

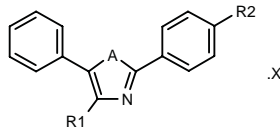
280525

N,N-Dimethyl-4-(4,5-diphenyl-1H-imidazol-2-yl)aniline

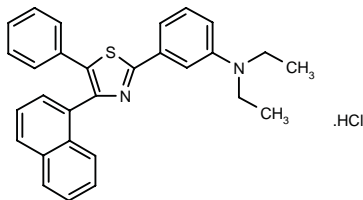


C23 H21 N3; Mol wt: 339.4399

ACTION – Selective corticotropin-releasing factor (or hormone) receptor CRF₂ (or CRH₂) antagonist. Other representative heterocyclic compounds include the following:



Compound	R1	R2	A	X	Formula
280526	2,3-(Me)2-Ph	N(Et)2	NH	HCl	C ₂₇ H ₂₉ N ₃ .HCl
280527	4-Pyr	N(Et)2	NH		C ₂₄ H ₂₄ N ₄
280529	1-Naph	N(CH ₂ CH ₂ OMe)2	NH	HCl	C ₃₁ H ₃₁ N ₃ O ₂ .HCl
280530	1-Naph	4-Me-1-Piz	S	HCl	C ₃₀ H ₂₇ N ₃ S.HCl



280528: C₂₉ H₂₆ N₂ S . HCl

Such compounds are considered to have potential in the treatment of anxiety, depression, anorexia nervosa, Alzheimer’s disease, hypertension, angina pectoris, irritable bowel syndrome, bronchial asthma, migraine, etc.

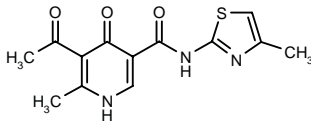
SOURCE – Yamanouchi.

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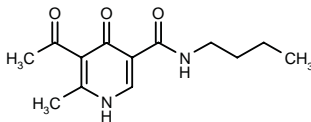
280611

5-Acetyl-6-methyl-N-(4-methylthiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxamide



C13 H13 N3 O3 S; Mol wt: 291.3297

ACTION – Highly selective ligand for brain GABA_A receptors expected to be useful in the treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancing memory. Another specifically claimed compound from this series of substituted 1,4-dihydro-4-oxonicotinic carboxamides is:



280613: C₁₃ H₁₈ N₂ O₃

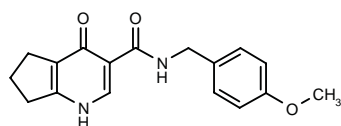
SOURCE – Neurogen.

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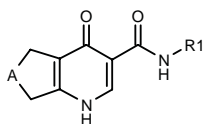
280615

N-(4-Methoxybenzyl)-4-oxo-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide



C17 H18 N2 O3; Mol wt: 298.3402

ACTION – Highly selective ligand for brain GABA_A receptors expected to be useful in the treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancing memory. Other specifically claimed compounds from this series of substituted cycloalkyl-4-oxonicotinic carboxamides include the following:



Compound	R1	A	Formula
280616	2-F-Ph	-(CH2)2-	C ₁₆ H ₁₅ FN ₂ O ₂
280618	4-MeO-Ph	-(CH2)2-	C ₁₇ H ₁₈ N ₂ O ₃
280619	3-OH-PhCH2	-(CH2)2-	C ₁₇ H ₁₈ N ₂ O ₃
280620	2-F-PhCH2	-(CH2)2-	C ₁₇ H ₁₇ FN ₂ O ₂
280621	CH2Ph	-CH2-	C ₁₆ H ₁₆ N ₂ O ₂
280623	Bu	-(CH2)3-	C ₁₅ H ₂₂ N ₂ O ₂
280624	CH2Ph	-(CH2)3-	C ₁₈ H ₂₀ N ₂ O ₂
280625	4-EtO-PhCH2	-(CH2)2-	C ₁₉ H ₂₂ N ₂ O ₃
280626	3-MeO-Ph	-CH2-	C ₁₆ H ₁₆ N ₂ O ₃

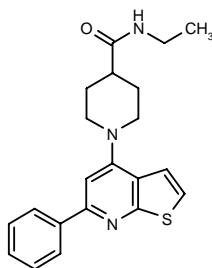
SOURCE – Neurogen.

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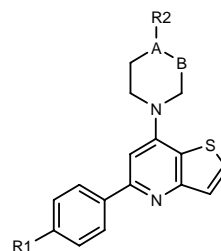
280824

N-Ethyl-1-(6-phenylthieno[2,3-*b*]pyridin-4-yl)piperidine-4-carboxamide



C21 H23 N3 O S; Mol wt: 365.4987

ACTION – Highly selective ligand for brain GABA_A receptors that interacts with the benzodiazepine binding site, expected to be useful in the treatment of anxiety, Down's syndrome, sleep, cognitive and seizure disorders, overdose with benzodiazepine drugs and for enhancing alertness. Other specifically claimed compounds within this series of heteroaryl fused pyridine derivatives include the following:



Compound	R1	R2	A	B	Formula
280837	H	H	-CH-	-NHCH2-	C ₁₈ H ₁₉ N ₃ S
280838	F	CONH-(CH2)3Cl	N	-CH2-	C ₂₁ H ₂₂ ClFN ₃ OS
280839	H	t-BuNHCO	-CH-	-CH2-	C ₂₃ H ₂₇ N ₃ OS
280840	H	CONH-CH2CH2OH	-CH-	-CH2-	C ₂₁ H ₂₃ N ₃ O ₂ S
280841	H	4-EtO-PhCH2	-CH-	-CH2-	C ₂₈ H ₂₈ N ₃ O ₂ S
280842	OEt	CONH2	-CH-	-CH2-	C ₂₁ H ₂₃ N ₃ O ₂ S
280843	F	CONH-CH2CH2OH	-CH-	-CH2-	C ₂₁ H ₂₂ FN ₃ O ₂ S

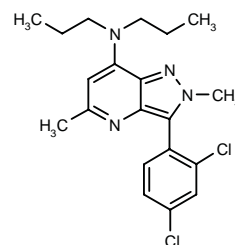
SOURCE – Neurogen.

REFERENCES

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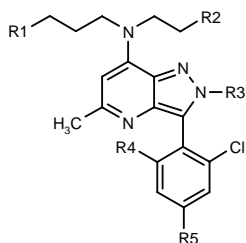
280915

N-[3-(2,4-Dichlorophenyl)-2,5-dimethyl-2*H*-pyrazolo[4,3-*b*]pyridin-7-yl]-*N,N*-dipropylamine

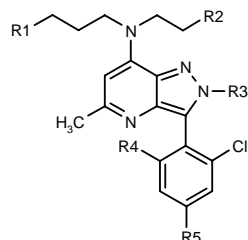


C20 H24 Cl2 N4; Mol wt: 391.3436

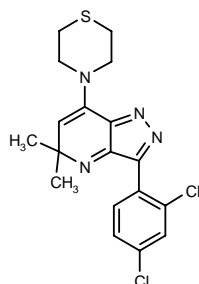
ACTION – Corticotropin-releasing factor (CRF) receptor antagonist ($K_i = 250$ nM or less) with potential in the treatment of disorders related to hypersecretion of CRF such as stress-related disorders, depression, anxiety and substance abuse. Other compounds from this series of pyrazolo[4,3-*b*]pyridines include the following:



Compound	R1	R2	Formula
280916	OMe	Pr	C ₂₁ H ₂₆ Cl ₂ N ₄ O
280917	H	4-Me-Ph	C ₂₄ H ₂₄ Cl ₂ N ₄



Compound	R1	R2	R3	R4	R5	Formula
280918	Me	H	Et	Me	Me	C ₂₃ H ₃₁ ClN ₄
280919	H	Me	Me	H	H	C ₂₀ H ₂₅ ClN ₄
280920	Me	Et	H	H	OMe	C ₂₂ H ₂₉ ClN ₄ O



280921: C₁₈ H₁₈ Cl₂ N₄ S

SOURCES – Janssen; Neurocrine Biosciences.

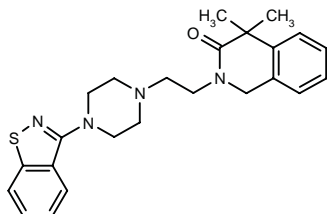
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ANTIPSYCHOTIC DRUGS

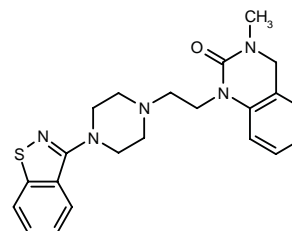
280306

2-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-one



C₂₄ H₂₈ N₄ O S; Mol wt: 420.5782

ACTION – Potent 5-HT_{1A} and 5-HT_{2A} receptor ligand selected for preclinical development as a potential atypical antipsychotic agent. Another related compound within this series of 1,2-benzisoxazole and 1,2-benzisothiazole piperazine derivatives is:



280307: C₂₂ H₂₅ N₅ O S

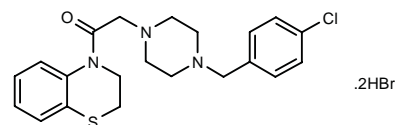
SOURCE – FAES.

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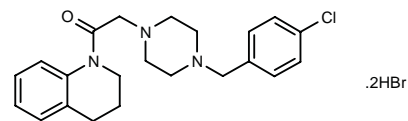
280368

2-[4-(4-Chlorobenzyl)piperazin-1-yl]-1-(2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethan-1-one dihydrobromide



C₂₁ H₂₄ Cl N₃ O S . 2HBr; Mol wt: 563.7834

ACTION – Agent for the treatment of CNS disorders including schizophrenia, mania, depression, anxiety, dementia, Parkinson's disease, tardive dyskinesias, drug abuse, obsessive-compulsive disorder and motor disorders associated with the use of neuroleptic agents, a highly potent and selective dopamine D₄ receptor antagonist (K_i = 14.2 nM) with markedly lower affinity for D₂ receptors (K_i = 10,000 nM). Another compound from this series of benzylpiperazinyl- and benzylpiperidinyl-ethanone derivatives is:



280369: C₂₂ H₂₆ Cl N₃ O . 2HBr

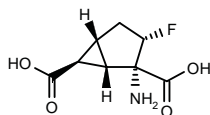
SOURCE – Neurogen.

REFERENCES

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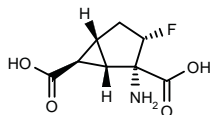
280539

(1*S*,2*S*,3*S*,5*R*,6*S*)-2-Amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



C₈H₁₀F N O₄; Mol wt: 203.1680

ACTION – Potent group II metabotropic glutamate receptor (mglu₂/mglu₃) agonist with potential in the treatment or prevention of schizophrenia, anxiety, depression, bipolar disorder, epilepsy, drug addiction, cognitive disorders, Alzheimer's disease, Huntington's chorea, Parkinson's disease, motor disorders associated with muscular stiffness, cerebral ischemia and spinal cord and brain lesions. Compound was shown to inhibit forskolin-stimulated cAMP accumulation in mglu₂-expressing CHO cells with an ED₅₀ of 23.65 nM, and it potentially inhibited methamphetamine-induced hyperlocomotion in mice (ED₅₀ = 0.05 mg/kg p.o.). Another compound from this series of fluorine-containing amino acid derivatives is:



280540: C₈H₁₀F N O₄

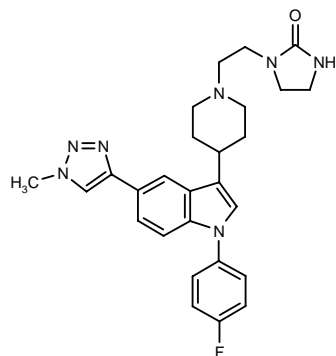
SOURCE – Taisho.

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281092

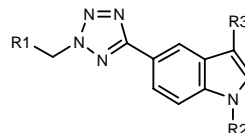
1-[2-[4-[1-(4-Fluorophenyl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]imidazolidin-2-one



C₂₇H₃₀F N₇ O; Mol wt: 487.5800

ACTION – An analogue of sertindole with highly increased affinity and selectivity for α_1 -adrenoceptors relative to dopamine D₂ and 5-HT_{2A} receptors, as demonstrated in binding assays by IC₅₀ values of 0.72, 450 and 220 nM, respectively, as compared to respective IC₅₀ values of 3.4, 4.1 and 0.39 nM for sertindole. Potentially useful for the treatment of psychosis, mania, benign prostatic hyper-

plasia, hypertension, cardiac arrhythmias and for reducing intraocular pressure. Other compounds from this series of 5-heteroaryl substituted indoles include the following:



Compound	R1	R2	R3	Formula
281095	H	4-Pyr	1-(2-oxo-1-imidazolidinyl-CH ₂ CH ₂)-1,2,3,6-tetrahydro-4-Pyr	C ₂₅ H ₂₇ N ₉ O
281098	H	4-Pyr	1-(2-oxo-1-imidazolidinyl-CH ₂ CH ₂)-4-Pip	C ₂₅ H ₂₉ N ₉ O
281101	H	4-F-Ph	1-(1-Me-1H-tetrazolyl-5-yl-CH ₂ CH ₂)-1,2,3,6-tetrahydro-4-Pyr	C ₂₉ H ₂₉ FN ₁₀ O ₄
281102	Me	4-F-Ph	1-(2-oxo-1-imidazolidinyl-CH ₂ CH ₂)-1,2,3,6-tetrahydro-4-Pyr	C ₂₇ H ₂₉ FN ₈ O
281103	H	4-F-Ph	1-Me-4-Pip	C ₂₂ H ₂₃ FN ₆

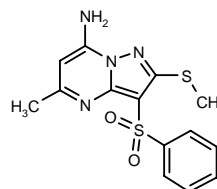
SOURCE – Lundbeck.

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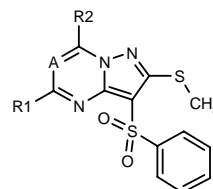
281151

5-Methyl-2-(methylsulfanyl)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-7-amine



C₁₄H₁₄N₄O₂S₂; Mol wt: 334.4226

ACTION – Agent for the treatment or prevention of CNS disorders such as psychosis, schizophrenia, depression, neurological disorders, memory disorders, Alzheimer's disease, Parkinson's disease, Huntington's chorea and amyotrophic lateral sclerosis with selective affinity for 5-HT₆ receptors. Other specifically claimed compounds from this series of pyrazolopyrimidines and pyrazolotriazines include the following:



Compound	R1	R2	A	Formula
281152	Me	1-Piz	CH	C ₁₈ H ₂₁ N ₅ O ₂ S ₂
281153	cyclopropyl	4-Me-1-Piz	CH	C ₂₁ H ₂₅ N ₅ O ₂ S ₂
281154	H	NH ₂	N	C ₁₂ H ₁₁ N ₅ O ₂ S ₂

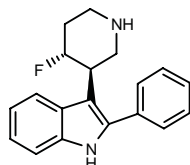
SOURCE – Roche.

REFERENCES

1. Boes, M. et al. (F. Hoffmann-La Roche AG) *Pyrazolopyrimidines and pyrazolotriazines with 5-HT_{2A} receptor affinity*. EP 941994.

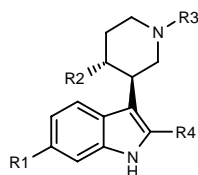
281314

(+)-3-[4(*R**)-Fluoropiperidin-3(*R**)-yl]-2-phenyl-1*H*-indole



C19 H19 F N₂; Mol wt: 294.3711

ACTION – Antipsychotic agent that acts as a selective antagonist at human 5-HT_{2A} receptors (K_i = 100 nM or less in CHO cells) with reduced extrapyramidal side effects due to its lack of dopamine D₂ receptor-antagonist effect. Other representative compounds within this series of 3-(piperidin-3-yl)indole derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
281315	H	F	H	4-F-Ph	(+)-(3 <i>R</i> *,4 <i>R</i> *)	C ₁₉ H ₁₈ F ₂ N ₂
281316	H	F	Me	Ph	(3 <i>R</i> ,4 <i>R</i>)	C ₂₀ H ₂₁ FN ₂
281317	F	F	H	3-furyl	(3 <i>R</i> *,4 <i>R</i> *)	C ₁₇ H ₁₆ F ₂ N ₂ O
281318	F	F	H	cyclohexyl-NHCO	(3 <i>R</i> *,4 <i>R</i> *)	C ₂₀ H ₂₅ F ₂ N ₃ O
281319	H	OH	H	Ph	(3 <i>R</i> *,4 <i>R</i> *)	C ₁₉ H ₂₀ N ₂ O

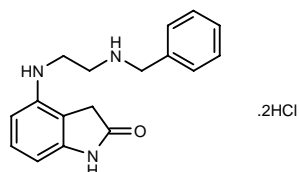
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Hallett, D.J. and Rowley, M. (Merck Sharp & Dohme Ltd.) *Indole derivs. as 5-HT_{2A} receptor antagonists*. WO 9947511.

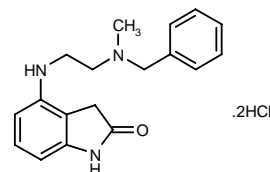
281882

4-[2-(Benzylamino)ethylamino]-2,3-dihydro-1*H*-indol-2-one dihydrochloride



C17 H19 N₃ O . 2HCl; Mol wt: 354.2789

ACTION – A selective dopamine autoreceptor agonist, as demonstrated in a binding assay in rat striatal brain tissue using [³H]-quinpirole as the ligand (IC₅₀ = 13.2 nM), with relatively much lower affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 892 nM against [³H]-spiroperidol binding in limbic brain tissue). Potentially useful for the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome and alcohol or drug addiction. Another specifically claimed compound from this series of 4-(aminoethylamino)-1,3-dihydro-2*H*-indol-2-one derivatives is:



281883: C18 H21 N₃ O . 2HCl

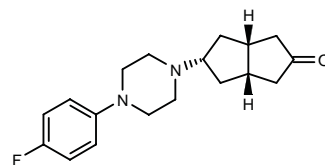
SOURCE – American Home Products.

REFERENCES

1. Nelson, J.A. et al. (American Home Products Corp.) *4-Amino-(ethylamino)-oxindole dopamine autoreceptor agonists*. WO 9952870.

282451

(3α,5β,6α)-5-[4-(4-Fluorophenyl)piperazin-1-yl]perhydropentalen-2-one



C18 H23 F N₂ O; Mol wt: 302.3907

ACTION – Agent for the treatment of CNS disorders such as psychosis, schizophrenia, Parkinson's disease, tardive dyskinesia, extrapyramidal side effects from neuroleptic agents, nausea and emesis with selective affinity for dopamine D₄ receptors. A representative compound from a series of bicyclic substituted piperazine-, piperidine- and tetrahydropyridine derivatives.

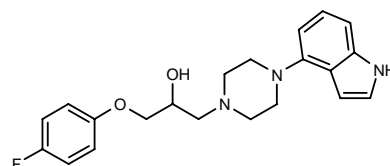
SOURCE – Pfizer.

REFERENCES

1. Filiri, A.F.J. and Butler, T.W. (Pfizer Products Inc.) *Bicyclic subst. piperazine-, piperidine- and tetrahydropyridine derivs., their preparation and their use as agents with central dopaminergic (dopamine D₄ receptor) activity*. EP 953567.

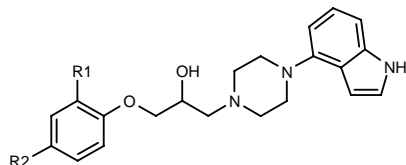
282465

1-(4-Fluorophenoxy)-3-[4-(1*H*-indol-4-yl)piperazin-1-yl]propan-2-ol



C21 H24 F N₃ O₂; Mol wt: 369.4376

ACTION – Antipsychotic agent that acts as a dopamine D₂ receptor antagonist and 5-HT_{1A} receptor antagonist or agonist, with very high affinity for both receptors ($K_i = 10.4$ nM). In addition to schizophrenia, it may be useful for the treatment of Alzheimer's disease, Parkinson's disease, depression and anxiety. Other exemplified indole derivatives include the following:



Compound	R1	R2	Formula
282466	H	Cl	C ₂₁ H ₂₄ ClN ₃ O ₂
282467	H	OMe	C ₂₂ H ₂₇ N ₃ O ₃
282468	Cl	H	C ₂₁ H ₂₄ ClN ₃ O ₂

SOURCE – American Home Products.

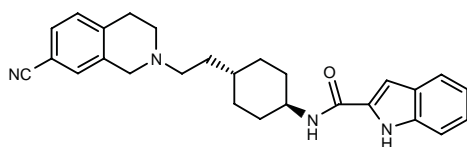
REFERENCES

1. Kelly, M.G. and Kang, Y.H. (American Home Products Corp.) *Antipsychotic indolyl derivs.* WO 9955672.

SB-269652

280646

trans-N-[4-[2-(7-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-1*H*-indole-2-carboxamide



C27 H30 N4 O; Mol wt: 426.5610

ACTION – Antipsychotic agent expected to be devoid of side effects normally associated with dopamine receptor antagonists, a potent and selective dopamine D₃ receptor antagonist ($pK_i = 8.67$ and 6.97 for D₃ and D₂ receptors, respectively) proven to block the decrease in dopamine release induced by the dopamine agonist quinlorane *in vivo* (3 mg/kg p.o.) in the rat nucleus accumbens, but not in striatum. At doses of 1.9-18.5 mg/kg p.o., it did not affect amphetamine-induced hyperactivity in rats and it did not induce catalepsy at up to 92.5 mg/kg. p.o.

SOURCE – SmithKline Beecham.

REFERENCES

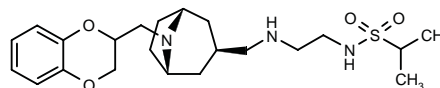
1. Branch, C.L. et al. (SmithKline Beecham plc) *Tetrahydroisoquinoline derivs. as modulators of dopamine D₃ receptors.* WO 9850364.

2. Taylor, S.G. et al. *SB-269652 is a selective D₃ receptor antagonist in vitro and in vivo.* Eur Neuropsychopharmacol 1999, 9(Suppl. 5): Abst P.2.038.

TREATMENT FOR MOOD DISORDERS

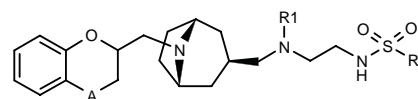
280421

exo-N-[2-[8-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-ylmethylamino]ethyl]propane-2-sulfonamide



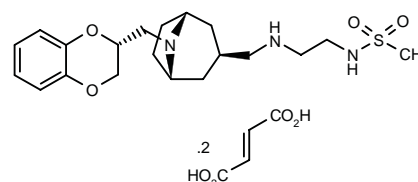
C22 H35 N3 O4 S; Mol wt: 437.6015

ACTION – Agent with potent affinity for α_{2B} -adrenoceptors ($pIC_{50} = 9.41$) and 1549-fold selectivity over α_{2D} -adrenoceptors ($pIC_{50} = 6.22$). Other compounds from this series of cyclic amine derivatives include the following:



.X

Compound	R1	R2	A	X	Formula
280422	Me	Me	O		C ₂₁ H ₃₃ N ₃ O ₄ S
280423	H	Ph	O		C ₂₅ H ₃₃ N ₃ O ₄ S
280424	H	Me	CH2	difumarate	C ₂₁ H ₃₃ N ₃ O ₃ S.2C ₄ H ₄ O ₄



280425: C20 H31 N3 O4 S . 2 C4 H4 O4

Central α_{2B} -adrenoceptor antagonists may have potential in the treatment of depression, hypotension and the like, peripheral antagonists may have potential in the treatment of gastrointestinal disorders, hypertension, obesity, diabetes, lower urinary tract disorders, etc., and α_{2B} -adrenoceptor agonists may be useful in the treatment of hypertension, glaucoma and the like.

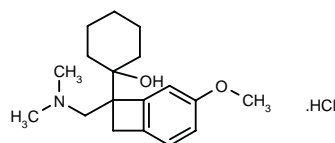
SOURCE – Hokuriku.

REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *Cyclic amine derivs.* JP 99180979.

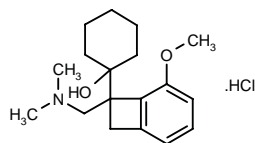
280913

1-[7-(Dimethylaminomethyl)-4-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]cyclohexanol hydrochloride



C₁₈ H₂₇ N O₂ . HCl; Mol wt: 325.8772

ACTION – 5-HT and norepinephrine reuptake inhibitor with potential in the treatment of depression, panic attacks, obsessive-compulsive disorder, phobia, drug abuse and anxiety. Antidepressant activity was demonstrated in the forced swimming test in mice at 10 mg/kg s.c., being clearly more potent than fluoxetine at the same dose. Another specifically claimed compound is:



280914: C₁₈ H₂₇ N O₂ . HCl

SOURCE – ADIR.

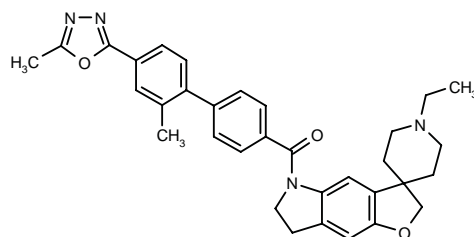
REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) *Benzocyclobutan cpds., their process for preparation and pharmaceutical compns. containing them.* CA 2264372, EP 940386, FR 2775687, JP 99310557.

SB-236057*

241202

1'-Ethyl-5-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-ylcarbonyl]-2,3,6,7-tetrahydro-5H-spiro[furo[2,3-f]indole-3,4'-piperidine]



C₃₃ H₃₄ N₄ O₃; Mol wt: 534.6640

ACTION – High-affinity ligand for human 5-HT_{1B} receptors (pK_i = 8.2) with > 100-fold selectivity over other 5-HT receptors including human 5-HT_{1D} receptors (pK_i = 6.3), as well as against a range of other receptors, ion channels and enzymes. In functional studies of [³⁵S]-GTPγS binding to human 5-HT_{1B} receptors stably expressed in CHO cells, compound exhibited inverse agonist activity (pEC₅₀ = 8.0) and caused a rightward shift of the 5-HT concentration-response curve, consistent with competitive antagonism (pA₂ = 8.9). In addition, it potentiated [³H]-5-HT release from electrically stimulated superfused guinea pig or human cortical slices in a concentration-dependent

manner, an effect which was significant at 100-1000 nM, indicating blockade of 5-HT terminal autoreceptors. Potentially useful for the treatment of depression and anxiety.

SOURCE – SmithKline Beecham.

REFERENCES

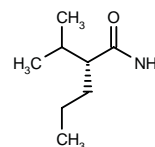
1. Gaster, L.M. et al. (SmithKline Beecham plc) *Tetracyclic spiro cpds., process for their preparation and their use as 5HT_{1D} receptor antagonists.* EP 799226, JP 98510821, US 5972951, WO 9619477.
2. Middlemiss, D.N. *New ligands for the study of 5-HT receptors.* J Psychopharmacol 1999, 13(3, Suppl. A): Abst S23.
3. Middlemiss, D.N. et al. *SB-236057, a selective 5-HT_{1B} receptor inverse agonist, blocks the 5-HT human terminal autoreceptor.* Eur J Pharmacol 1999, 375(1-3): 359.
4. SmithKline Beecham Annual Report 1996.

*Identified compound **241202** (see **239037**) Drug Data Rep 1996, 018(10): 0866.

NEUROLOGIC DRUGS**ANTIEPILEPTIC DRUGS****(R)-PID**

280345

2(R)-Isopropylpentanamide



C₈ H₁₇ N O; Mol wt: 143.2283

ACTION – Antiepileptic agent, a valpromide derivative with anticonvulsant activity in mice (ED₅₀ = 58 and 49 mg/kg i.p. against maximal electroshock- and pentylenetetrazol-induced seizures, respectively). At the active anticonvulsant doses, compound did not produce sedative effects, with an ED₅₀ of 99 mg/kg i.p. for inducing ataxia in the rotarod test in mice. Compound showed a favorable pharmacokinetic profile, with a plasma half life of 2.4 h. Unlike valpromide, it was not metabolized to its homologous acid.

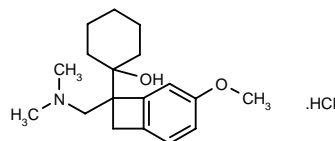
SOURCE – Hebrew University, Jerusalem (IL).

REFERENCES

1. Bialer, M. et al. (Yissum Research Development Co.) *Propylisopropyl acetic acid and propylisopropyl acetamide stereoisomers, a method for their synthesis and pharmaceutical compns. containing them.* WO 9954282.
2. Haj-Yehia, A. and Blaler, M. *Structure-pharmacokinetic relationship in a series of valpromide derivatives with antiepileptic activity.* Pharm Res 1989, 6(8): 683.
3. Spiegelstein, O. et al. *Stereoselective pharmacokinetics and pharmacodynamics of propylisopropyl acetamide - A CNS active chiral analogue of valproic acid.* Epilepsia 1999, 40(Suppl. 2): 248.
4. Spiegelstein, O. et al. *Stereoselective pharmacokinetics and pharmacodynamics of propylisopropyl acetamide, a CNS-active chiral amide analog of valproic acid.* Pharm Res 1999, 16(10): 1582.

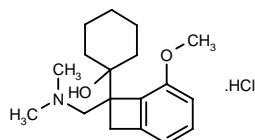
280913

1-[7-(Dimethylaminomethyl)-4-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]cyclohexanol hydrochloride



C₁₈ H₂₇ N O₂ . HCl; Mol wt: 325.8772

ACTION – 5-HT and norepinephrine reuptake inhibitor with potential in the treatment of depression, panic attacks, obsessive-compulsive disorder, phobia, drug abuse and anxiety. Antidepressant activity was demonstrated in the forced swimming test in mice at 10 mg/kg s.c., being clearly more potent than fluoxetine at the same dose. Another specifically claimed compound is:



280914: C₁₈ H₂₇ N O₂ . HCl

SOURCE – ADIR.

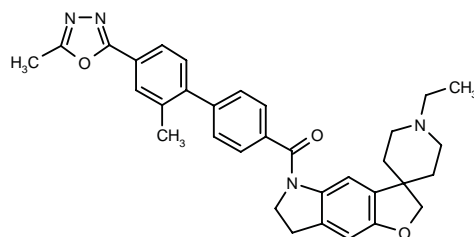
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1. Peglion, J.-L. et al. (ADIR et Cie.) *Benzocyclobutan cpds., their process for preparation and pharmaceutical compns. containing them.* CA 2264372, EP 940386, FR 2775687, JP 99310557.

SB-236057*

241202

1'-Ethyl-5-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-ylcarbonyl]-2,3,6,7-tetrahydro-5H-spiro[furo[2,3-f]indole-3,4'-piperidine]



C₃₃ H₃₄ N₄ O₃; Mol wt: 534.6640

ACTION – High-affinity ligand for human 5-HT_{1B} receptors (pK_i = 8.2) with > 100-fold selectivity over other 5-HT receptors including human 5-HT_{1D} receptors (pK_i = 6.3), as well as against a range of other receptors, ion channels and enzymes. In functional studies of [³⁵S]-GTPγS binding to human 5-HT_{1B} receptors stably expressed in CHO cells, compound exhibited inverse agonist activity (pEC₅₀ = 8.0) and caused a rightward shift of the 5-HT concentration-response curve, consistent with competitive antagonism (pA₂ = 8.9). In addition, it potentiated [³H]-5-HT release from electrically stimulated superfused guinea pig or human cortical slices in a concentration-dependent

manner, an effect which was significant at 100-1000 nM, indicating blockade of 5-HT terminal autoreceptors. Potentially useful for the treatment of depression and anxiety.

SOURCE – SmithKline Beecham.

REFERENCES

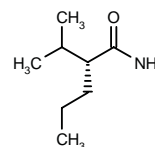
1. Gaster, L.M. et al. (SmithKline Beecham plc) *Tetracyclic spiro cpds., process for their preparation and their use as 5HT_{1D} receptor antagonists.* EP 799226, JP 98510821, US 5972951, WO 9619477.
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4. SmithKline Beecham Annual Report 1996.

*Identified compound **241202** (see **239037**) Drug Data Rep 1996, 018(10): 0866.

NEUROLOGIC DRUGS**ANTIEPILEPTIC DRUGS****(R)-PID**

280345

2(R)-Isopropylpentanamide



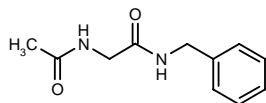
C₈ H₁₇ N O; Mol wt: 143.2283

ACTION – Antiepileptic agent, a valpromide derivative with anticonvulsant activity in mice (ED₅₀ = 58 and 49 mg/kg i.p. against maximal electroshock- and pentylenetetrazol-induced seizures, respectively). At the active anticonvulsant doses, compound did not produce sedative effects, with an ED₅₀ of 99 mg/kg i.p. for inducing ataxia in the rotarod test in mice. Compound showed a favorable pharmacokinetic profile, with a plasma half life of 2.4 h. Unlike valpromide, it was not metabolized to its homologous acid.

SOURCE – Hebrew University, Jerusalem (IL).

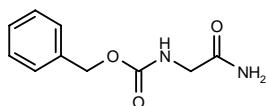
REFERENCES

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2. Haj-Yehia, A. and Blaler, M. *Structure-pharmacokinetic relationship in a series of valpromide derivatives with antiepileptic activity.* Pharm Res 1989, 6(8): 683.
3. Spiegelstein, O. et al. *Stereoselective pharmacokinetics and pharmacodynamics of propylisopropyl acetamide - A CNS active chiral analogue of valproic acid.* Epilepsia 1999, 40(Suppl. 2): 248.
4. Spiegelstein, O. et al. *Stereoselective pharmacokinetics and pharmacodynamics of propylisopropyl acetamide, a CNS-active chiral amide analog of valproic acid.* Pharm Res 1999, 16(10): 1582.

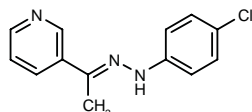
280450***N*²-Acetyl-*N*¹-benzylglycinamide**

C11 H14 N2 O2; Mol wt: 206.2436

ACTION – Anticonvulsant proven active in the maximal electroshock (MES) seizure test in mice (ED_{50} = 88 mg/kg i.p.) and showing neurotoxicity only at much higher doses (TD_{50} > 200 mg/kg i.p.). Half-life was 2.1 ± 0.4 h following i.v. administration to dogs. Claimed for controlling epileptic seizures, febrile convulsions and convulsions precipitated by brain lesions, as well as for the treatment and/or prevention of bipolar disease, migraine and chronic pain. Another specifically claimed compound is:

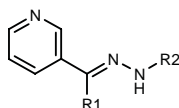
**280452:** C10 H12 N2 O3**SOURCE** – Yissum.**REFERENCES**

1. Bialer, M. et al. (Yissum Research Development Co.) *Anticonvulsant drugs and pharmaceutical compsns. thereof*. WO 9943309.

280686**1-(3-Pyridinyl)ethan-1-one *N*-(4-chlorophenyl)hydrazone**

C13 H12 Cl N3; Mol wt: 245.7118

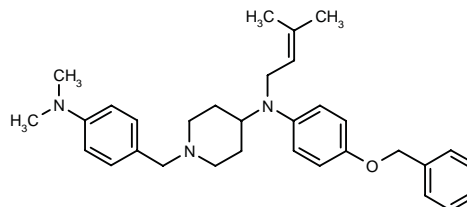
ACTION – Anticonvulsant that acts as an excitatory amino acid (EAA) antagonist; its activity was demonstrated in the maximal electroshock (MES) seizure test in mice following i.p. administration and in rats following oral administration, where it exhibited an ED_{50} value of 7.79 mg/kg p.o. Lack of neurotoxicity was demonstrated in the rotarod test in rats (TD_{50} > 500 mg/kg p.o.). Potentially useful in the treatment of epilepsy, stroke and Parkinson's disease. Within this series of hydrazones, hydrazines, semicarbazones and thiosemicarbazones derived from pyridyl ketones, the following compounds are also included:



Compound	R1	R2	Formula
280687	Me	3,4-(Cl)2-Ph	C ₁₃ H ₁₁ Cl ₂ N ₃
280688	Ph	CONH2	C ₁₃ H ₁₂ N ₄ O

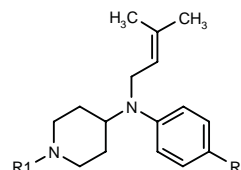
SOURCE – K&K Biosciences.**REFERENCES**

1. Kadaba, P.K. and Lin, Z. (K&K Biosciences, Inc.) *Hydrazones, hydrazines, semicarbazones and thiosemicarbazones derived from pyridyl ketones as anticonvulsant drugs and excitatory amino acid antagonists*. US 5942527.

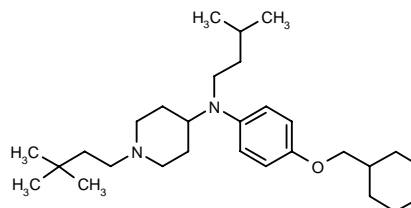
280722***N*-(4-Benzyloxyphenyl)-*N*-[1-[4-(dimethylamino)-benzyl]piperidin-4-yl]-*N*-(3-methyl-2-butenyl)amine**

C32 H41 N3 O; Mol wt: 483.6959

ACTION – N-type calcium channel blocker, as demonstrated *in vitro* by inhibition of Ca²⁺ influx in IMR-32 cells (IC_{50} = 0.33 μ M). *In vivo*, it completely protected DBA/2 mice against sound-induced seizures at 10 mg/kg i.v. Potentially useful for the treatment of epilepsy, stroke, cerebral ischemia, head trauma, pain, asthma and amyotrophic lateral sclerosis. Other compounds from this series of heterocyclic-substituted aniline derivatives include the following:



Compound	R1	R2	Formula
280725	i-BuCH ₂	OCH ₂ Ph	C ₂₈ H ₄₀ N ₂ O
280727	t-BuCH ₂ CH ₂	OCH ₂ Ph	C ₂₉ H ₄₂ N ₂ O
280729	4-OH-PhCH ₂	OCH ₂ Ph	C ₃₀ H ₃₆ N ₂ O ₂
280732	2-pyrrolyl-CH ₂	OCH ₂ Ph	C ₂₈ H ₃₆ N ₃ O
280733	4-imidazolyl-CH ₂	OCH ₂ Ph	C ₂₇ H ₃₄ N ₄ O
280737	1-(i-BuCH ₂)-4-i-Pr-2-Piz-CO	OCH ₂ Ph	C ₃₆ H ₅₄ N ₄ O ₂
280739	CH ₂ Ph	OCH ₂ Ph	C ₃₀ H ₃₆ N ₂ O
280740	CH ₂ CH ₂ CH(OH)Me	OCH ₂ Ph	C ₂₇ H ₃₈ N ₂ O ₂
280741	t-BuCH ₂ CH ₂	i-Pr	C ₂₅ H ₄₂ N ₂
280742	4-N(Me)2-PhCH ₂	t-BuCH ₂ CH ₂	C ₃₁ H ₄₇ N ₃
280745	(S)-i-BuCH(OH)CO	OCH ₂ Ph	C ₂₉ H ₄₀ N ₂ O ₃

**280743:** C29 H50 N2 O

SOURCE – Warner-Lambert.

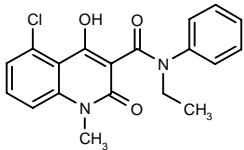
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THERAPY OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

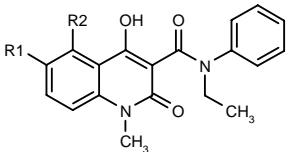
282472

5-Chloro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-1,2-dihydroquinoline-3-carboxamide



C19 H17 Cl N2 O3; Mol wt: 356.8073

ACTION – Agent for the treatment of autoimmune diseases, particularly useful for the treatment of multiple sclerosis and its manifestations. It was effective in acute experimental autoimmune encephalomyelitis (EAE) in mice, a model of multiple sclerosis, producing 96-98% inhibition of EAE at doses of 1-5 mg/kg p.o., and it was practically devoid of embryotoxicity in rats at doses of 6-30 mg/kg s.c. Other specifically claimed quinoline derivatives include the following:



Compound	R1	R2	Formula
282474	H	OMe	C ₂₀ H ₂₀ N ₂ O ₄
282475	H	Br	C ₁₉ H ₁₇ BrN ₂ O ₃
282476	-OCH ₂ O-		C ₂₀ H ₁₈ N ₂ O ₅

SOURCE – Active Biotech.

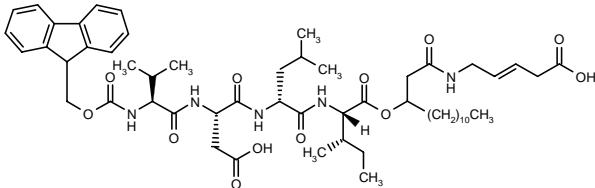
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COGNITION-ENHANCING DRUGS

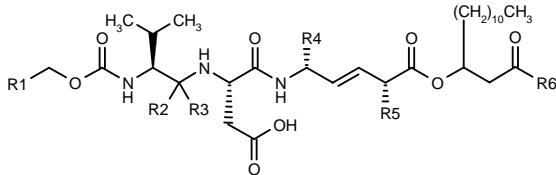
280111

5-[3-(9*H*-Fluoren-9-ylmethoxycarbonyl-L-valyl-L-aspartyl-D-leucyl-L-isoleucyloxy)tetradecanamido]-3(*E*)-pentenoic acid

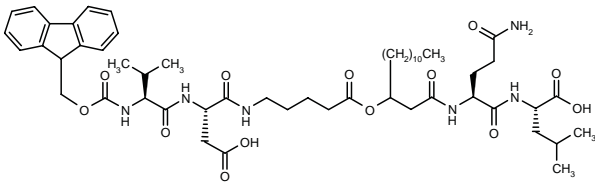


C55 H81 N5 O12; Mol wt: 1004.2680

ACTION – Agent for the treatment of dementia and hyperlipidemia that acts by promoting the production of apolipoprotein E, as shown in HepG2 cells (327% increase at 1 μM relative to control = 100%). Other exemplified depsipeptides include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
280112	Ph	-O-	H	H	H	-L-Gln-OEt	C ₄₃ H ₆₇ N ₅ O ₁₂
280113	Ph	-O-	H	H	H	-L-Gln-OH	C ₄₁ H ₆₃ N ₅ O ₁₂
280114	9-fluorenyl	-O-	i-Bu	Me	H	-L-Gln-L-Leu-OH	C ₅₉ H ₈₈ N ₆ O ₁₃
280116	9-fluorenyl	H	H	H	H	OH	C ₄₃ H ₆₁ N ₃ O ₉



280115: C54 H80 N6 O13

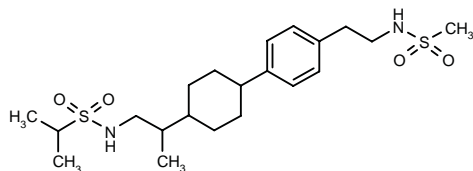
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Yanai, M. et al. (Nisshin Flour Milling Co., Ltd.) *Depsipeptides containing non-natural amino acids*. EP 931792.

280252

N-[2-[4-[4-[2-(Methylsulfonamido)ethyl]phenyl]-cyclohexyl]propyl]propane-2-sulfonamide



C21 H36 N2 O4 S2; Mol wt: 444.6574

ACTION – Agent reported to potentiate agonist-induced excitability of human glutamate (AMPA) GluR4B receptors in cells and thus expected to potentiate glutamate receptor function *in vivo* and exhibit ampakine-like behavior. Potentially useful in the treatment of a wide range of conditions including cognitive disorders, neurodegenerative disorders such as Alzheimer's disease, age-related dementia and memory impairment, movement disorders such as tardive dyskinesia, Huntington's chorea, myoclonus and Parkinson's disease, sexual dysfunction, depression, attention deficit disorder and attention deficit hyperactivity disorder, and psychosis. A specifically claimed compound from a series of sulfonamide derivatives.

SOURCE – Lilly.

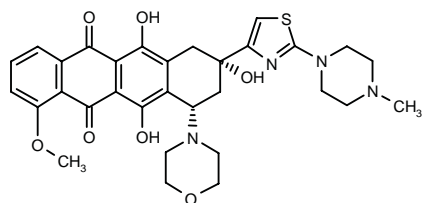
REFERENCES

1. Escribano, A.M. et al. (Eli Lilly and Company) *Sulphonamide derivs.* EP 937708, WO 9943285.

280952

(8*S*,10*S*)-6,8,11-Trihydroxy-1-methoxy-8-[2-(4-methylpiperazin-1-yl)thiazol-4-yl]-10-(4-morpholinyl)-5,7,8,9,10,12-hexahydronaphthacene-5,12-dione

7-Deoxy-9-deacetyl-9-[2-(4-methylpiperazin-1-yl)thiazol-4-yl]-7-(4-morpholinyl)daunomycinone



C31 H34 N4 O7 S; Mol wt: 606.6966

ACTION – A specifically claimed compound from a series of 9-heterocyclyl anthracyclinone derivatives that inhibits the formation of amyloid deposits by amyloidogenic proteins and induces the degradation of existing amyloid deposits. It produced 49.2% inhibition of the seed-triggered aggregation of Aβ1-40 peptide monomer. Potentially useful in the treatment or prevention of amyloidotic diseases such as systemic amyloidoses and amyloidoses of the peripheral and central nervous system, the latter including Alzheimer's disease, Down's syndrome, spongiform encephalopathies and the like.

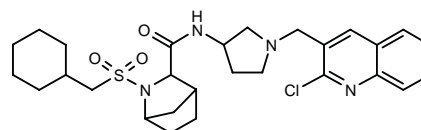
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Mantegani, S. et al. (Pharmacia & Upjohn SpA) *Heterocyclyl anthracyclinone derivs.* WO 9946253.

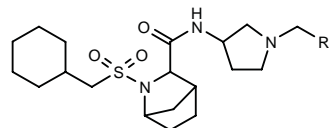
281576

N-[1-(2-Chloroquinolin-3-ylmethyl)pyrrolidin-3-yl]-2-(cyclohexylmethylsulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide



C28 H37 Cl N4 O3 S; Mol wt: 545.1443

ACTION – An inhibitor of the rotamase activity of the FK-506-binding protein FKBP-12 that lacks inhibitory activity against the protein phosphatase calcineurin, useful as a neurotrophic agent in the treatment of neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, without exhibiting immunosuppressive activity. Other compounds from this series of 2-azabicyclo[2.2.1]heptane derivatives include the following:



Compound	R1	Formula
281577	3-indolyl	C ₂₇ H ₃₈ N ₄ O ₃ S
281578	3-Pyr	C ₂₄ H ₃₆ N ₄ O ₃ S

SOURCE – Pfizer.

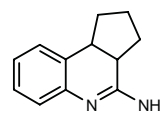
REFERENCES

1. Nagel, A.A. and Blake, J.F. (Pfizer Products Inc.) *2-Aza-bicyclo[2.2.1]heptane derivs. and their use as rotamase inhibitors.* CA 2266565, EP 947506.

TREATMENT OF CEREBROVASCULAR DISEASES

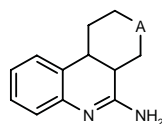
280054

2,3,3a,9b-Tetrahydro-1*H*-cyclopenta[*c*]quinolin-4-amine



C12 H14 N2; Mol wt: 186.2566

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of neurodegenerative, inflammatory, autoimmune and cardiovascular disorders. Other specifically claimed compounds from this series of 3,4-dihydroquinoline derivatives include the following:



Compound	A	Formula
280055	-CH ₂ -	C ₁₃ H ₁₆ N ₂
280056	-(CH ₂) ₂ -	C ₁₄ H ₁₈ N ₂

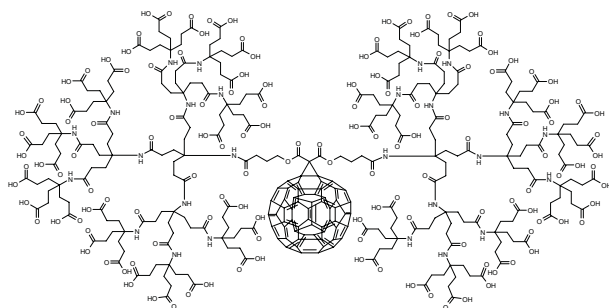
SOURCE – Schering AG.

REFERENCES

1. Jaroch, S. et al. (Schering AG) *3,4-Dihydroquinoline derivs. as nitrogen monoxide synthase (NOS) inhibitors*. DE 19806348, WO 9941240.

280447

54-Cascade:Methanofullerene[2]:(2-aza-7-oxa-3,8-dioxooctylidene):(2-aza-3-oxopentylidene)2:propionic acid



C331 H404 N26 O138; Mol wt: 6954.8760

ACTION – Neuroprotective agent with radical-scavenging activity, a dendrimeric fullerene derivative with highly improved water solubility as compared to previously reported fullerenes by virtue of the presence of the protic group-containing dendrons.

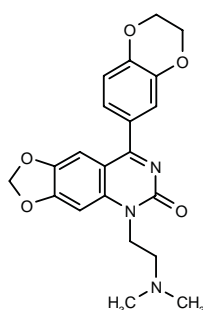
SOURCE – Aventis R&T.

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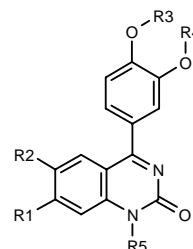
280957

8-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5-[2-(dimethyl-amino)ethyl]-1,3-dioxolo[4,5-*g*]quinazolin-6(5*H*)-one



C21 H21 N3 O5; Mol wt: 395.4129

ACTION – AMPA receptor antagonist giving an IC₅₀ value of 0.2 μM in an electrophysiological assay using AMPA receptors expressed in oocytes and an ED₅₀ of 1 mg/kg i.v. in the maximal electroshock (MES) seizure test in mice. Potentially useful for the treatment of neuronal damage following global and focal ischemia, the treatment or prevention of neurodegenerative conditions and the treatment of epilepsy, cognition disorders, schizophrenia, Parkinson's disease and myoclonus, as well as pain. Other representative compounds from this series of quinazolines include the following:



Compound	R1	R2	R3	R4	R5	Formula
280958	-OCH ₂ O-	-(CH ₂) ₂ -			Et	C ₁₉ H ₁₆ N ₂ O ₅
280959	-OCH ₂ O-	-CH ₂ -			CH ₂ CH ₂ N(Me) ₂	C ₂₀ H ₁₉ N ₃ O ₅
280960	-N(Me)COO-	-CH ₂ -			i-Pr	C ₂₀ H ₁₇ N ₃ O ₅
280961	-OCH ₂ O-	-CH ₂ -			i-Pr	C ₁₉ H ₁₆ N ₂ O ₅

SOURCE – CoCensys.

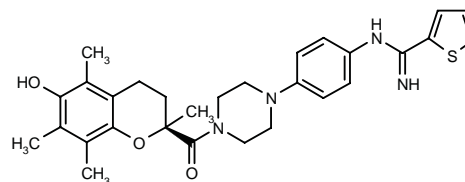
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1. Upasani, R. et al. (CoCensys, Inc.) *Substd. quinazolines and analogs and the use thereof*. WO 9944612.

BN-80933

266384

N¹-[4-[4-[6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2(*S*)-ylcarbonyl]piperazin-1-yl]phenyl]-thiophene-2-carboxamide



C29 H34 N4 O3 S; Mol wt: 518.6786

ACTION – Potent and selective nitric oxide synthase (NOS) inhibitor with high selectivity for neuronal NOS (nNOS; K_i = 0.92 μM) over the endothelial (eNOS) and inducible (iNOS) forms of the enzyme (K_i = 111 and > 300 μM, respectively); its potency and selectivity were confirmed in functional experiments by inhibition of electrical field stimulation-induced relaxation of rat gastric fundus (nNOS-mediated effect; IC₅₀ = 18 μM) but not of endothelium-dependent, carbachol-induced relaxation of rat aorta (eNOS-mediated effect) at up to 300 μM. Compound also showed antioxidant properties, as demonstrated by both inhibition of iron-dependent lipid peroxidation in rat brain membranes (IC₅₀ = 0.29 μM) and inhibition of glutamate-induced oxidative stress in HT-22 cells (IC₅₀ = 0.13 μM). *In vivo*, it was neuroprotective in a

model of transient cerebral ischemia in rats, where doses of 0.3-10 mg/kg i.v. at 4 and 24 h after ischemia induced a significant and long-lasting reduction in infarct volume (> 60% protection) and improvement in neurological scores; when compound was given up to 8 h after the onset of ischemia, significant improvement in neurological outcome was seen. The neuroprotective activity of compound was confirmed in models of global ischemia in gerbils and a mouse head trauma model. Potentially useful for the treatment of stroke, trauma and neuro-degenerative disorders.

SOURCE – Beaufour-Ipsen.

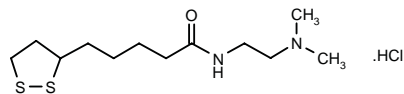
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- Auguet, M. et al. *New potent neuroprotective agents are inhibitors of neuronal nitric oxide synthase (NOS) and scavengers of oxygen free radicals. In vivo studies (I).* Soc Neurosci Abst 1998, 24(Part 1): Abst 483.8.
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- Demerlé-Pallardy, C. et al. *Neuroprotection by BN 80933 against oxidative stress on a mouse hippocampal cell line and hypoxia on primary cortical neuronal cultures.* Soc Neurosci Abst 1999, 25(Part 2): Abst 837.12.
- Spinnewyn, B. et al. *Neuroprotection afforded by BN 80933: A free radical scavenger and a NO-synthase inhibitor after reversible focal ischemia in rat.* J Cereb Blood Flow Metab 1999, 19(Suppl. 1): Abst 223.

LA-PLUS

280944

N-[2-(Dimethylamino)ethyl]-5-(1,2-dithiolan-3-yl)-pentanamide hydrochloride



C12 H24 N2 O S2 . HCl; Mol wt: 312.9275

ACTION – Lipoic acid analogue, the decarboxylation product of the naturally occurring form of lipoic acid lipoyllysine. It penetrates and diffuses into cells by crossing biological membranes, and is then enzymatically reduced and, in contrast to lipoic acid, retained inside the cell, exerting potent antioxidant effects. LA-PLUS was shown to completely block glutamate-induced apoptosis in mouse neuronal HT4 cells at a concentration of 50 µM, whereas lipoic acid did not provide total protection even at a concentration of 100 µM. The compound was also much more effective than lipoic acid in downregulating PMA-induced ICAM-1 expression in human endothelial cells and in enhancing glucose uptake by L6 myoblasts.

Methods of treating conditions involving reactive oxygen species or a redox mechanism such as degenerative brain disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy), neoplastic diseases, cerebral ischemia, diabetes, atherosclerosis, autoimmune diseases, hepatic disorders, trauma, cachexia and AIDS, are specifically claimed.

SOURCE – University of California, Oakland, Oakland, CA (US).

REFERENCES

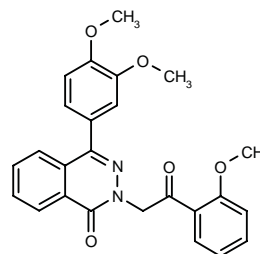
- Packer, L. et al. (University of California, Oakland) *Lipoic acid analogs.* WO 9945922.

RESPIRATORY DRUGS

ASTHMA THERAPY

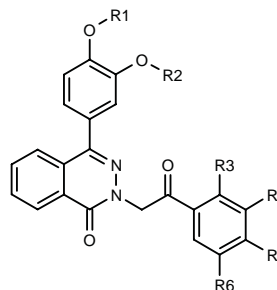
280158

4-(3,4-Dimethoxyphenyl)-2-[2-(2-methoxyphenyl)-2-oxoethyl]-1(2*H*)-phthalazinone



C25 H22 N2 O5; Mol wt: 430.4578

ACTION – Selective inhibitor of phosphodiesterase type 4 (PDE4; $-\log IC_{50} = 7.52$) with low toxicity and high oral bioavailability, potentially useful in the treatment of asthma and other respiratory tract disorders, and dermatoses. Within this series of phthalazinone derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
280159	Et	Me	H	H	H	H	C ₂₄ H ₂₀ N ₂ O ₄
280160	Me	Et	H	H	H	H	C ₂₅ H ₂₂ N ₂ O ₄
280161	Me	cyclopentyl	H	H	H	H	C ₂₈ H ₂₆ N ₂ O ₄
280162	Me	CHF2	H	H	H	H	C ₂₄ H ₁₈ F ₂ N ₂ O ₄
280163	Me	Me	OMe	H	H	OMe	C ₂₆ H ₂₄ N ₂ O ₆
280164	Me	Me	H	Cl	NH2	Cl	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₄

model of transient cerebral ischemia in rats, where doses of 0.3-10 mg/kg i.v. at 4 and 24 h after ischemia induced a significant and long-lasting reduction in infarct volume (> 60% protection) and improvement in neurological scores; when compound was given up to 8 h after the onset of ischemia, significant improvement in neurological outcome was seen. The neuroprotective activity of compound was confirmed in models of global ischemia in gerbils and a mouse head trauma model. Potentially useful for the treatment of stroke, trauma and neuro-degenerative disorders.

SOURCE – Beaufour-Ipsen.

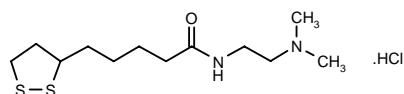
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LA-PLUS

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SOURCE – University of California, Oakland, Oakland, CA (US).

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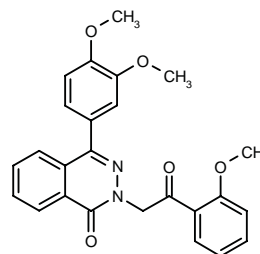
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RESPIRATORY DRUGS

ASTHMA THERAPY

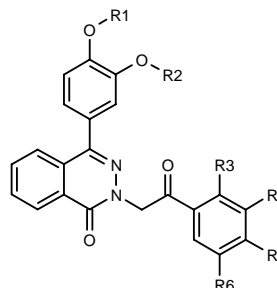
280158

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280159	Et	Me	H	H	H	H	C ₂₄ H ₂₀ N ₂ O ₄
280160	Me	Et	H	H	H	H	C ₂₅ H ₂₂ N ₂ O ₄
280161	Me	cyclopentyl	H	H	H	H	C ₂₈ H ₂₆ N ₂ O ₄
280162	Me	CHF2	H	H	H	H	C ₂₄ H ₁₈ F ₂ N ₂ O ₄
280163	Me	Me	OMe	H	H	OMe	C ₂₆ H ₂₄ N ₂ O ₆
280164	Me	Me	H	Cl	NH2	Cl	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₄

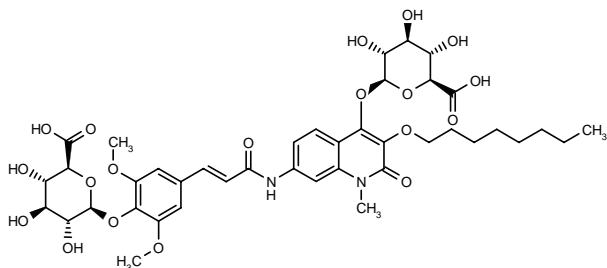
SOURCE – Byk Gulden.

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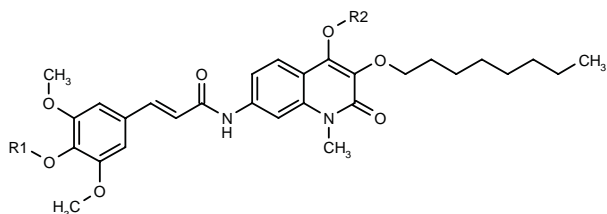
280166

1-O-[7-[3-[4-(β-D-Glucopyranos-1-O-yluronic acid)-3,5-dimethoxyphenyl]-2(*E*)-propenamido]-1-methyl-3-octyloxy-2-oxo-1,2-dihydroquinolin-4-yl]-β-D-glucopyranuronic acid



C41 H52 N2 O19; Mol wt: 876.8568

ACTION – Antiallergic agent for the treatment or prevention of both immediate and delayed-type allergic diseases, proven active in a rat passive cutaneous anaphylaxis (PCA) reaction (54% inhibition at 0.5 mg/kg i.v.; tranilast: 52% inhibition at 100 mg/kg p.o.). Compound also exhibited dose-dependent inhibition of ovalbumin-induced immediate and delayed-type asthmatic reactions in sensitized guinea pigs, giving 29 and 64% inhibition, respectively, at 0.2 mg/kg i.v. and 37 and 73% inhibition, respectively, at 0.5 mg/kg i.v.; in this model, prednisolone at 10 mg/kg p.o. gave 27 and 69% inhibition, respectively. LD₅₀ > 2000 mg/kg p.o. in mice. Other compounds within this series of quinolinone glycoside derivatives include the following:



Compound	R1	R2	Formula
280167	H	β-D-glucopyranos-1-O-yluronic acid	C ₃₅ H ₄₄ N ₂ O ₁₃
280168	β-D-glucopyranosyl	β-D-glucopyranosyl	C ₄₁ H ₅₆ N ₂ O ₁₇
280169	β-D-galactopyranosyl	β-D-galactopyranosyl	C ₄₁ H ₅₆ N ₂ O ₁₇
280170	α-D-mannopyranosyl	α-D-mannopyranosyl	C ₄₁ H ₅₆ N ₂ O ₁₇

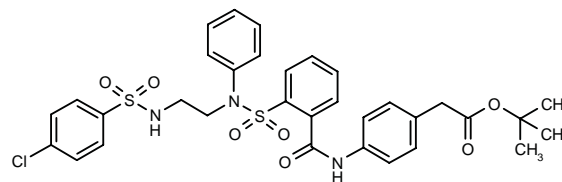
SOURCE – Dainippon Ink & Chemicals.

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1. Takagaki, H. et al. (Dainippon Ink & Chemicals, Inc.) *Quinolinone glycoside, production process, and anti-allergic agent*. CA 2259784, EP 933378, JP 99269191.

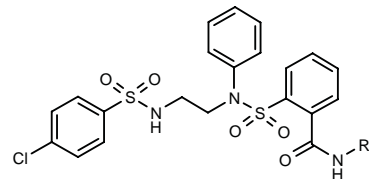
280418

2-[4-[2-[*N*-(2-(4-Chlorophenylsulfonamido)ethyl)-*N*-phenylsulfamoyl]benzamido]phenyl]acetic acid *tert*-butyl ester



C33 H34 Cl N3 O7 S2; Mol wt: 684.2306

ACTION – Antiallergic and antiasthmatic agent proven to selectively inhibit the release of eosinophil peroxidase from fMLP-stimulated guinea pig eosinophils *in vitro* (90.8% inhibition at 0.01 μM). *In vivo*, it produced 58.3 and 90.8% inhibition, respectively, of the increase in airways resistance induced by antigen inhalation in sensitized guinea pigs at 3 and 10 mg/kg p.o. Within this series of sulfonamide derivatives, the following are also included:



Compound	R1	Formula
280419	4-CO ₂ Et-Ph	C ₃₀ H ₂₆ ClN ₃ O ₇ S ₂
280420	2-CO ₂ H-PhSO ₂ N(Ph)CH ₂ CH ₂	C ₃₆ H ₃₃ ClN ₄ O ₉ S ₃

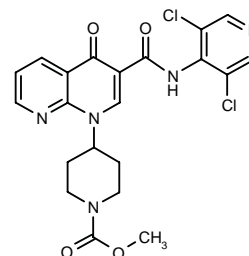
SOURCE – Kaken.

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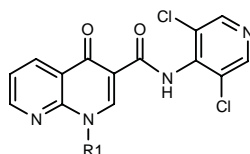
280504

4-[3-[*N*-(3,5-Dichloropyridin-4-yl)carbamoyl]-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]piperidine-1-carboxylic acid methyl ester



C21 H19 Cl2 N5 O4; Mol wt: 476.3181

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.0009 μM) and of the production of TNF (IC₅₀ = 0.0002 μM in lipopolysaccharide-stimulated murine macrophages), a representative compound from a series of 1-cycloalkyl-1,8-naphthyridin-4-one derivatives, wherein the following are also included:



Compound	R1	Formula
280506	1-(PhCH ₂ OCO)-4-Pip	C ₂₇ H ₂₃ Cl ₂ N ₅ O ₄
280508	cyclopentyl	C ₁₉ H ₁₆ Cl ₂ N ₄ O ₂
280510	trans-4-(EtNHCONH)-cyclohexyl	C ₂₃ H ₂₄ Cl ₂ N ₆ O ₃
280511	tetrahydro-4-thiopyranyl	C ₁₉ H ₁₆ Cl ₂ N ₄ O ₂ S
280513	4-morpholinyl	C ₁₈ H ₁₅ Cl ₂ N ₅ O ₃

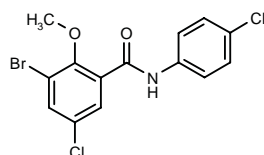
SOURCE – Suntory.

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1. Shimamoto, T. et al. (Suntory Ltd.) *1-Cycloalkyl-1,8-naphthyridin-4-one derivs. with phosphodiesterase IV inhibitory activity*. WO 9938867.

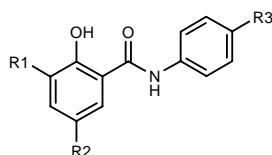
280536

3-Bromo-5-chloro-*N*-(4-chlorophenyl)-2-methoxybenzamide



C₁₄ H₁₀ Br Cl₂ N O₂; Mol wt: 375.0480

ACTION – Antiinflammatory agent, a selective calcium (Ca²⁺) release-activated calcium (Ca²⁺) channel (CRACC) inhibitor. Other compounds from this series of aniline derivatives include the following:



Compound	R1	R2	R3	Formula
280537	H	OMe	Cl	C ₁₄ H ₁₂ ClNO ₃
280538	Br	Cl	Me	C ₁₄ H ₁₁ BrClNO ₂

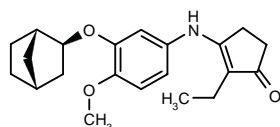
SOURCE – Yamanouchi.

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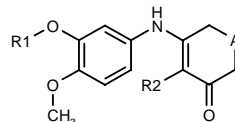
280553

exo-3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenylamino]-2-ethyl-2-cyclopenten-1-one



C₂₁ H₂₇ N O₃; Mol wt: 341.4483

ACTION – Antiallergic and antiinflammatory agent, a phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 80 nM against enzyme from rat neutrophils). *In vivo*, compound was shown to potently inhibit TPA-induced ear edema in mice. No mortality was observed following i.p. administration of 30 mg/kg to mice. Other compounds from this series of 3-anilino-2-cycloalkenone derivatives include the following:



Compound	R1	R2	A	Formula
280555	2-indanyl	Me	CH ₂	C ₂₃ H ₂₅ NO ₃
280557	cyclopentyl	H	NH	C ₁₇ H ₂₂ N ₂ O ₃

Certain compounds of the invention were shown to inhibit neutrophil activation and proved active against antigen-induced bronchoconstriction in sensitized guinea pigs and/or against DNFB-induced contact dermatitis in mice, while exhibiting low acute toxicity in mice.

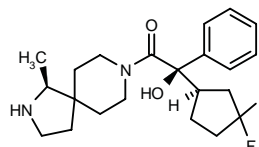
SOURCE – Nikken Chemicals.

REFERENCES

1. Ina, M. et al. (Nikken Chemicals Co., Ltd.) *3-Anilino-2-cycloalkenone derivs*. JP 99189577.

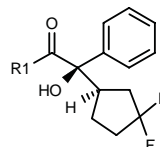
280633

2(*R*)-[3,3-Difluorocyclopent-1(*R*)-yl]-2-hydroxy-1-[1(*S**)-methyl-2,8-diazaspiro[4.5]dec-8-yl]-2-phenylethan-1-one



C₂₂ H₃₀ F₂ N₂ O₂; Mol wt: 392.4870

ACTION – Agent for the treatment of respiratory, urological and digestive disorders, a potent and selective muscarinic M₃ receptor antagonist, as demonstrated in binding studies (K_i = 0.26 nM vs. 21 nM for M₂ receptors; ratio M₂/M₃ = 80). Compound exhibited good bronchodilating activity in the methacholine inhalation test in dogs at 0.1 mg/kg p.o. Within this series of *N*-acyl cyclic amine derivatives, the following are also included:



Compound	R1	Formula
280634	4-(NH ₂ CH ₂ CH ₂)-1-Pip	C ₂₀ H ₂₈ F ₂ N ₂ O ₂
280635	2,8-diazaspiro[4.5]dec-8-yl	C ₂₁ H ₂₈ F ₂ N ₂ O ₂
280636	(3aR*,8aS*)-perhydropyrrolo-[3,4-d]azepin-2-yl	C ₂₁ H ₂₈ F ₂ N ₂ O ₂
280637	perhydropyrrolo[3,4-c]pyrrol-2-yl	C ₁₉ H ₂₄ F ₂ N ₂ O ₂

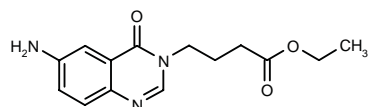
SOURCE – Banyu.

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1. Tsuchiya, Y. et al. (Banyu Pharmaceutical Co., Ltd.) *N-Acyl cyclic amine derivs.* WO 9940070.

280780

4-(6-Amino-4-oxo-3,4-dihydroquinazolin-3-yl)butanoic acid ethyl ester



C14 H17 N3 O3; Mol wt: 275.3063

White solid, *m.p.* 64 °C.

ACTION – Antiinflammatory agent, an inhibitor of TNF- α production (IC_{50} = 4 μ M in lipopolysaccharide [LPS]-stimulated human peripheral blood mononuclear cells). *In vivo* in an acute lung inflammation model, when given by inhalation to LPS-treated mice, it was able to reduce TNF- α contents in bronchoalveolar lavage fluid in a dose-dependent manner at doses ranging from 3.9 to 10 mg/ml.

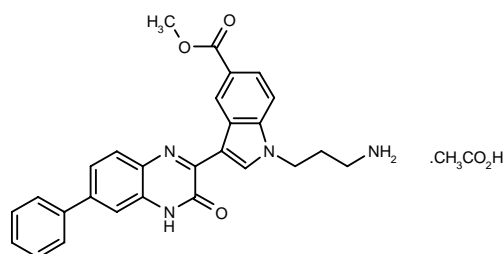
SOURCE – University of California, San Diego, San Diego, CA (US).

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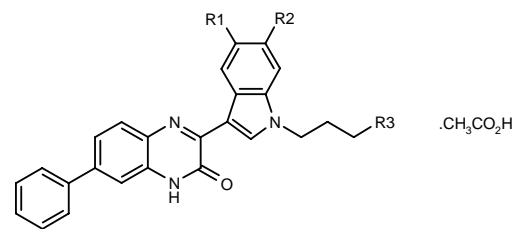
280967

1-(3-Aminopropyl)-3-(3-oxo-6-phenyl-3,4-dihydroquinoxalin-2-yl)-1*H*-indole-5-carboxylic acid methyl ester acetate



C27 H24 N4 O3 . C2 H4 O2; Mol wt: 512.5632

ACTION – Protein kinase C (PKC) inhibitor, particularly useful in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or neurodegenerative disorders. It also inhibits one or more of the following cytokines: IL-1 β , TNF- α , granulocyte-macrophage colony-stimulating factor and IL-8. In particular, it has potential for the oral or topical treatment of inflammatory airways or atopic diseases such as asthma, bronchitis, rhinitis and atopic dermatitis, inflammatory bowel disease, autoimmune diseases, e.g., multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus or rheumatoid arthritis, malignant diseases, HIV infection and for preventing transplant rejection. Other preferred compounds from this series of quinoxalinones are:



Compound	R1	R2	R3	Formula
280968	H	OCH2Ph	NH2	C ₃₂ H ₂₈ N ₄ O ₂ ·C ₂ H ₄ O ₂
280969	OCH2Ph	H	NH2	C ₃₂ H ₂₈ N ₄ O ₂ ·C ₂ H ₄ O ₂
280970	Br	H	NH2	C ₂₅ H ₂₁ BrN ₄ O·C ₂ H ₄ O ₂
280971	H	H	CH2NH2	C ₂₆ H ₂₄ N ₄ O·C ₂ H ₄ O ₂
280972	H	H	NH2	C ₂₅ H ₂₂ N ₄ O·C ₂ H ₄ O ₂

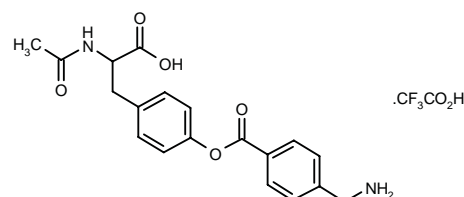
SOURCE – AstraZeneca.

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1. Karabelas, K. et al. (Astra AB) *New cpds.* WO 9946260.

282384

N-Acetyl-4-*O*-[4-(aminomethyl)benzoyl]-DL-tyrosine trifluoroacetate



C19 H20 N2 O5 . C2 H F3 O2; Mol wt: 470.3979

ACTION – Trypsin inhibitor that exhibits high efficacy in inhibiting the enzyme, as well as selectivity over trypsin; potentially useful in the treatment of mast cell-mediated diseases such as asthma and other allergic and inflammatory conditions. It also displays greatly enhanced plasma stability ($t_{1/2}$ = 22 h on incubation in human plasma).

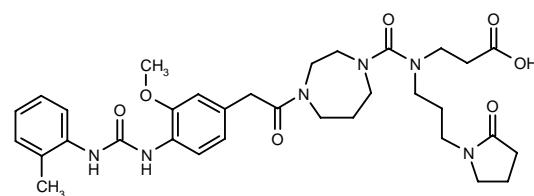
SOURCE – Protherics.

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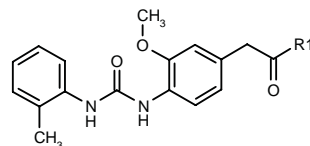
282488

3-[*N*-[4-[2-[3-Methoxy-4-[3-(2-methylphenyl)-ureido]phenyl]acetyl]perhydro-1,4-diazepin-1-ylcarbonyl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]amino]propionic acid

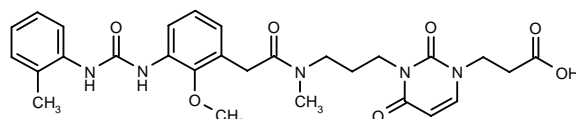


C33 H44 N6 O7; Mol wt: 636.7456

ACTION – Cell adhesion inhibitor with the ability to block the interaction of VCAM-1 with the integrin VLA-4 ($\alpha_4\beta_1$) and therefore potentially useful in the treatment or prevention of inflammatory disorders, particularly asthma, joint inflammation and inflammatory bowel disease. Other preferred compounds from this series of substituted diamines include the following:



Compound	R1	Formula
282489	(R)-NH(CH ₂) ₃ N(Me)-CONHCH(Me)CH ₂ CO ₂ H	C ₂₆ H ₃₅ N ₅ O ₆
282490	4-[(R)-CONHCH(Me)CH ₂ CO ₂ H]-perhydro-1,4-diazepin-1-yl	C ₂₇ H ₃₅ N ₅ O ₆
282491	3,4-(MeO) ₂ -PhCH ₂ CH ₂ N(CH ₂ CH ₂ -CO ₂ H)CON(Me)(CH ₂) ₃ N(Me)	C ₃₆ H ₄₇ N ₅ O ₈
282493	1-(CO ₂ HCH ₂ CH ₂)-4-Pip-CH ₂ NH	C ₂₆ H ₃₄ N ₄ O ₅
282494	1-[CO ₂ H(CH ₂) ₃ CO]-4-Pip-CH ₂ NH	C ₂₈ H ₃₆ N ₄ O ₆



282492: C₂₈ H₃₃ N₅ O₇

SOURCE – Rhône-Poulenc Rorer (Aventis).

REFERENCES

1. McCarthy, C. et al. (Rhône-Poulenc Rorer Ltd.) *Subst. diamines and their use as cell adhesion inhibitors*. WO 9954321.

SCH-55700

198457

Humanized monoclonal antibody to human IL-5 (hIL-5) that incorporates the antigen recognition sites for hIL-5 into consensus human IgG_{4/κ} constant regions using complementarity-determining region (CDR) grafting technology

CDP-835

ACTION – Humanized monoclonal antibody to human IL-5 with high-affinity binding to hIL-5 (K_d = 20 pmol/l) and proven to potently inhibit hIL-5 binding to Ba/F3 cells (IC_{50} = 0.5 nmol/l) and block the IL-5-mediated proliferation of human erythroleukemic TF-1 cells (IC_{50} = 45 pmol/l). In allergic mice, compound (0.1-10 mg/kg i.p. or i.m.) inhibited eosinophil influx into the lungs for up to 8 weeks after administration of the highest dose. It was able to block cutaneous eosinophilia in allergic rabbits (5 mg/kg i.v.), as well as pulmonary eosinophilia and neutrophilia (0.1-1 mg/kg i.p.) caused by tracheal injection of hIL-5 in guinea pigs. Moreover, in allergic cynomolgus monkeys, a single dose of 0.3 mg/kg i.v. was able to block, for up to 6 months, pulmonary eosinophilia caused by antigen challenge. Potentially useful for the treatment of bronchial asthma and as a pharmacological tool for elucidating the role of IL-5 in human eosinophilic diseases such as asthma. Currently in phase II trials.

SOURCES – Celltech Chiroscience; Schering-Plough.

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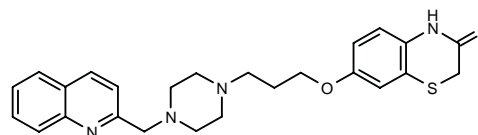
18. Celltech Group plc Annual Report 1997.

19. Schering-Plough Corp. Annual Report 1995.

VUF-K-8788*

273492

7-[3-[4-(2-Quinolinylmethyl)-1-piperazinyl]propoxy]-3,4-dihydro-2H-1,4-benzothiazin-3-one



C₂₅ H₂₈ N₄ O₂ S; Mol wt: 448.5882

ACTION – Antiallergic agent proven to inhibit histamine-induced bronchoconstriction in guinea pigs (0.3-1 mg/kg p.o.), anaphylactic bronchoconstriction in passively sensitized guinea pigs (ED_{50} = 0.023 mg/kg p.o.) and both the immediate- and late-phase asthmatic reaction in actively sensitized guinea pigs (0.3-1 mg/kg p.o.); for comparison, the reference antihistamine terfenadine was less potent against histamine-induced bronchoconstriction (3 mg/kg p.o.), showed somewhat less activity in passively sensitized guinea pigs (ED_{50} = 0.29 mg/kg p.o.) and was active only against the immediate-phase asthmatic reaction. Compound was also able to inhibit macrophage and eosinophil infiltration into bronchoalveolar lavage fluid in allergic guinea pigs and to inhibit airways hyper-reactivity to acetylcholine in actively sensitized guinea pigs. Potentially useful for the treatment of bronchial asthma.

SOURCE – Kowa.

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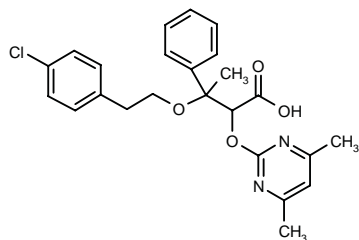
*Identified compound **273492** Drug Data Rep 1999, 021(04): 0315.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

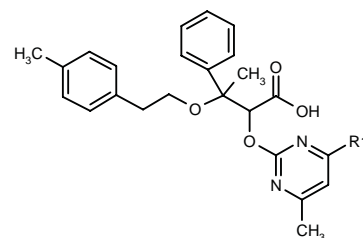
280945

3-[2-(4-Chlorophenyl)ethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3-phenylbutyric acid



C24 H25 Cl N2 O4; Mol wt: 440.9245

ACTION – Mixed endothelin ET_A/ET_B receptor antagonist with K_i values of 20 and 70 nM, respectively. Claimed for the treatment of chronic heart failure, myocardial infarction, atherosclerosis, arrhythmia, angina pectoris, restenosis, hypertension, pulmonary hypertension, renal failure, cerebral ischemia, asthma, benign prostatic hyperplasia and prostate cancer. Other compounds from this series of unsymmetrically substituted carboxylic acid derivatives include the following:



Compound	R1	Formula
280946	OMe	C ₂₅ H ₂₈ N ₂ O ₅
280947	Me	C ₂₅ H ₂₈ N ₂ O ₄

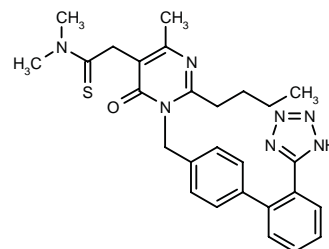
SOURCE – BASF.

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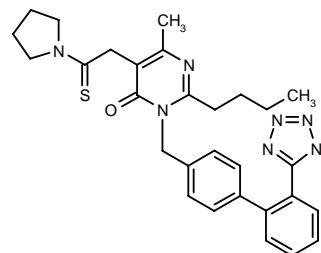
282470

2-[2-Butyl-4-methyl-6-oxo-1-[2'-(1H-1,2,3,4-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,6-dihydropyrimidin-5-yl]-N,N-dimethylthioacetamide



C27 H31 N7 O S; Mol wt: 501.6559

ACTION – Potent angiotensin II receptor antagonist proven to inhibit the pressor response to angiotensin II in conscious normotensive rats with an ID_{50} value of 1.10 mg/kg p.o., whereas it was devoid of acute toxicity in male and female mice at doses of up to 5000 mg/kg p.o. Potentially useful in the treatment of cardiovascular disorders. Another specifically claimed pyrimidone is:



282471: C29 H33 N7 O S

SOURCE – Boryung.

REFERENCES

1. Lee, J.-H. et al. (Boryung Pharmaceutical Co., Ltd.) *Pyrimidinone cpds., pharmaceutical compns. containing the cpds. and the process for preparing the same*. WO 9955681.

ACTION – Antiallergic agent proven to inhibit histamine-induced bronchoconstriction in guinea pigs (0.3-1 mg/kg p.o.), anaphylactic bronchoconstriction in passively sensitized guinea pigs (ED_{50} = 0.023 mg/kg p.o.) and both the immediate- and late-phase asthmatic reaction in actively sensitized guinea pigs (0.3-1 mg/kg p.o.); for comparison, the reference antihistamine terfenadine was less potent against histamine-induced bronchoconstriction (3 mg/kg p.o.), showed somewhat less activity in passively sensitized guinea pigs (ED_{50} = 0.29 mg/kg p.o.) and was active only against the immediate-phase asthmatic reaction. Compound was also able to inhibit macrophage and eosinophil infiltration into bronchoalveolar lavage fluid in allergic guinea pigs and to inhibit airways hyper-reactivity to acetylcholine in actively sensitized guinea pigs. Potentially useful for the treatment of bronchial asthma.

SOURCE – Kowa.

REFERENCES

1. Timmerman, H. et al. (Kowa Co., Ltd.) *Diamine derivs. and pharmaceutical containing the same*. EP 957100, WO 9902520.

2. Takizawa, T. et al. *Effects of a new antiallergic agent, VUF-K-8788, on experimental asthmatic reactions in guinea pigs*. Pharmacology 1999, 59(3): 127.

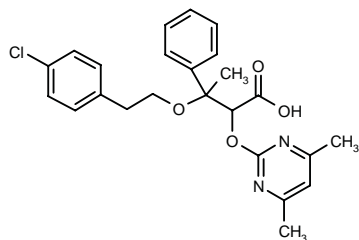
*Identified compound **273492** Drug Data Rep 1999, 021(04): 0315.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

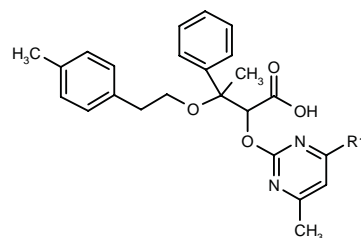
280945

3-[2-(4-Chlorophenyl)ethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3-phenylbutyric acid



C24 H25 Cl N2 O4; Mol wt: 440.9245

ACTION – Mixed endothelin ET_A/ET_B receptor antagonist with K_i values of 20 and 70 nM, respectively. Claimed for the treatment of chronic heart failure, myocardial infarction, atherosclerosis, arrhythmia, angina pectoris, restenosis, hypertension, pulmonary hypertension, renal failure, cerebral ischemia, asthma, benign prostatic hyperplasia and prostate cancer. Other compounds from this series of unsymmetrically substituted carboxylic acid derivatives include the following:



Compound	R1	Formula
280946	OMe	C ₂₅ H ₂₈ N ₂ O ₅
280947	Me	C ₂₅ H ₂₈ N ₂ O ₄

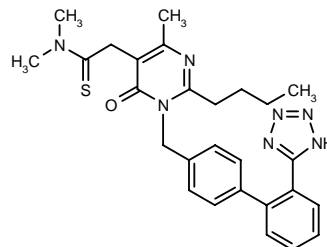
SOURCE – BASF.

REFERENCES

1. Amberg, W. et al. (BASF AG) *Novel unsymmetrically substd. carboxylic acid derivs., method for producing them, and their use as mixed ET_A/ET_B* . WO 9944998.

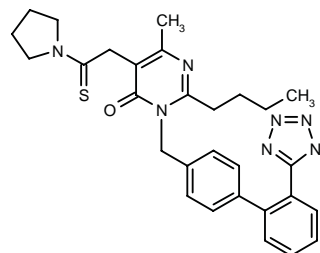
282470

2-[2-Butyl-4-methyl-6-oxo-1-[2'-(1H-1,2,3,4-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,6-dihydropyrimidin-5-yl]-N,N-dimethylthioacetamide



C27 H31 N7 O S; Mol wt: 501.6559

ACTION – Potent angiotensin II receptor antagonist proven to inhibit the pressor response to angiotensin II in conscious normotensive rats with an ID_{50} value of 1.10 mg/kg p.o., whereas it was devoid of acute toxicity in male and female mice at doses of up to 5000 mg/kg p.o. Potentially useful in the treatment of cardiovascular disorders. Another specifically claimed pyrimidone is:



282471: C29 H33 N7 O S

SOURCE – Boryung.

REFERENCES

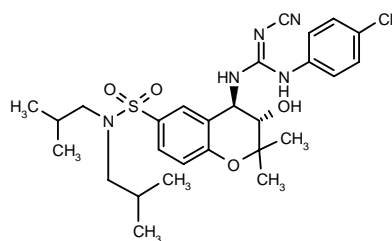
1. Lee, J.-H. et al. (Boryung Pharmaceutical Co., Ltd.) *Pyrimidinone cpds., pharmaceutical compns. containing the cpds. and the process for preparing the same*. WO 9955681.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

280309

(3*S*,4*R*)-*N*-(4-Chlorophenyl)-*N'*-cyano-*N''*-[6-(diisobutylsulfamoyl)-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl]guanidine

(3*S*,4*R*)-4-[*N''*-(4-Chlorophenyl)-*N'*-cyanoguanidino]-3-hydroxy-*N,N*-bis(isobutyl)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-sulfonamide



C₂₇ H₃₆ Cl N₅ O₄ S; Mol wt: 562.1314

M.p. 145-8 °C, [α]_D +0.5° (*c* 0.37, MeOH).

ACTION – Cardioprotective agent able to increase the time to onset of contracture in globally ischemic perfused rat hearts (EC₂₅ = 0.04 μ M) while exhibiting low vaso-relaxant activity (IC₅₀ = 9.4 μ M for relaxation of rat aorta precontracted with methoxamine); its mechanism of action appears to involve opening of cardiac K_{ATP} channels.

SOURCE – Bristol-Myers Squibb.

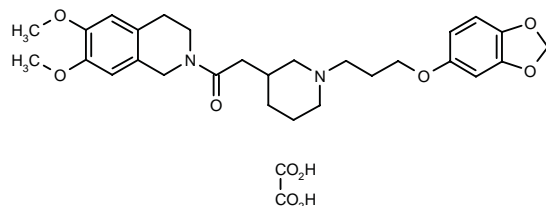
REFERENCES

1. Ding, C.Z. and Atwal, K.S. (Bristol-Myers Squibb Co.) *Sulfonamido subst. benzopyran potassium channel activators*. CA 2178353, EP 747374, JP 97003035, US 5869478.

2. Ding, C.Z. et al. *Cardioselective antiischemic ATP-sensitive potassium channel (K_{ATP}) openers. 6. Effect of modifications at C6 of benzopyranyl cyanoguanidines*. J Med Chem 1999, 42(18): 3711.

280546

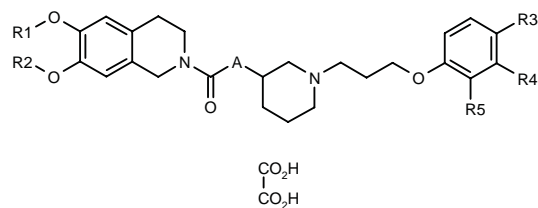
2-[1-[3-(1,3-Benzodioxol-5-yloxy)propyl]piperidin-3-yl]-1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-1-ethanone oxalate



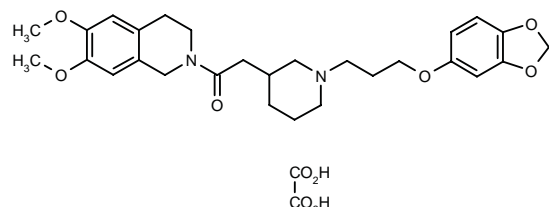
C₂₈ H₃₆ N₂ O₆ . C₂ H₂ O₄; Mol wt: 586.6342

ACTION – Agent with I₁ current-inhibitory and bradycardic activity and potential in the treatment of ischemic heart diseases such as angina pectoris and myocardial infarction, as well as other cardiovascular disorders such as congestive heart failure and arrhythmia. Other compounds from this series of 2-(piperidylalkylcarbonyl)-

1,2,3,4-tetrahydroisoquinoline derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
280547	Me	Me	Cl	H	H	CH ₂	C ₂₇ H ₃₆ ClN ₂ O ₄ ·C ₂ H ₂ O ₄
280548	Me	Me	H	H	Cl	CH ₂	C ₂₇ H ₃₆ ClN ₂ O ₄ ·C ₂ H ₂ O ₄
280550	Me	Me	-OCH ₂ O-	H	H	O	C ₂₇ H ₃₄ N ₂ O ₇ ·C ₂ H ₂ O ₄
280551	-CH ₂ -	-CH ₂ -	-OCH ₂ O-	H	H	CH ₂	C ₂₇ H ₃₂ N ₂ O ₆ ·C ₂ H ₂ O ₄



280549: C₂₈ H₃₆ N₂ O₆ . C₂ H₂ O₄

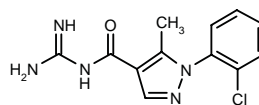
SOURCE – Yamanouchi.

REFERENCES

1. Kakefuda, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *2-(Piperidylalkylcarbonyl)-1,2,3,4-tetrahydroisoquinoline derivs. or their salts*. JP 99189593.

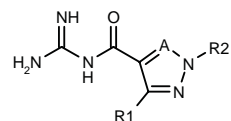
280879

N-[1-(2-Chlorophenyl)-5-methyl-1*H*-pyrazol-4-ylcarbonyl]-guanidine



C₁₂ H₁₂ Cl N₅ O; Mol wt: 277.7138

ACTION – Na⁺/H⁺ exchange type 1 (NHE-1) inhibitor with potential in the treatment of ischemia, particularly for the treatment of perioperative myocardial ischemic injury. Other specifically claimed compounds within this series of substituted guanidine derivatives include the following:



Compound	R1	R2	A	Formula
280880	H	6-quinolyl	C(Me)	C ₁₅ H ₁₄ N ₆ O
280881	Me	Ph	CH	C ₁₂ H ₁₃ N ₅ O
280882	Me	Ph	N	C ₁₁ H ₁₂ N ₆ O
280883	Me	1-Naph	N	C ₁₅ H ₁₄ N ₆ O
280885	H	2-CF ₃ -Ph	C(cyclopropyl)	C ₁₅ H ₁₄ F ₃ N ₅ O
280886	H	2-Cl-4-(MeSO ₂)-Ph	C(cyclopropyl)	C ₁₅ H ₁₆ ClN ₅ O ₃ S
280887	H	8-Br-5-quinolyl	C(cyclopropyl)	C ₁₇ H ₁₅ BrN ₆ O

SOURCE – Pfizer.

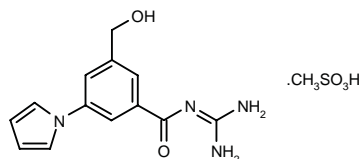
REFERENCES

1. Hamanaka, E.S. et al. (Pfizer Products Inc.) *N-[(Substd. five-membered di- or triaza diunsaturated ring)carbonyl] guanidine derivs. for the treatment of ischemia*. WO 9943663.

FR-168888

234448

N''-[3-(Hydroxymethyl)-5-(1*H*-pyrrol-1-yl)benzoyl]-guanidine methanesulfonate



C13 H14 N4 O2 . C H4 O3 S; Mol wt: 354.3852

ACTION – Cardioprotective agent, an inhibitor of Na⁺/H⁺ exchange ($K_i = 6.4$ nM in rat lymphocytes) proven to protect (0.032-0.32 mg/kg i.v.) rats against ventricular fibrillation induced by reperfusion after 5 min of regional ischemia, with efficacy superior to lidocaine. Compound (1.0-10 mg/kg i.v.) was also able to reduce the size of myocardial infarction induced by 60-min ischemia and 60-min reperfusion in rats, whereas propranolol and diltiazem did not show such cardioprotective effects, and it significantly reduced ventricular tachycardia and ventricular fibrillation during ischemia. Compound did not induce any change in hemodynamic parameters in rats.

SOURCE – Fujisawa.

REFERENCES

1. Kuno, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidine derivs. as inhibitors of Na⁺/H⁺ exchange in cells*. EP 699185, JP 96511243, US 5824691, WO 9426709.
2. Ohara, F. et al. *Protective effect of FR168888, a new Na⁺/H⁺ exchange inhibitor, on ischemia and reperfusion-induced arrhythmia and myocardial infarction in rats: In comparison with other cardioprotective compounds*. Jpn J Pharmacol 1999, 80(4): 295.
3. Ohara, F. et al. *Protective effects of a new Na⁺/H⁺ exchange inhibitor, FR168888, on cardiac ischemia-reperfusion injury in rats and dogs*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-1002.

MAB 166-32

280384

Monoclonal antibody to factor D

ACTION – Monoclonal antibody that specifically binds to factor D and blocks its ability to activate the alternative complement pathway. Claimed for the treatment of diseases or conditions mediated by excessive or uncontrolled activation of the complement system including tissue damage due to ischemia–reperfusion injury, inflammatory disorders such as septic shock, adult respiratory distress syndrome, asthma, Crohn's disease and pancreatitis, transplant rejection, adverse drug reactions and autoimmune diseases. Its activity and specificity were demonstrated in several *in vitro* assays by inhibition of complement-activated hemolysis and of the formation of C3a. In addition, it was shown to protect rabbit hearts against human complement-mediated tissue

damage in an *ex vivo* model following perfusion with human plasma when given at 0.3 µg/ml, and it proved effective in an extracorporeal circulation model of human cardiopulmonary bypass, inhibiting both complement activation and platelet and neutrophil activation.

SOURCE – Tanox.

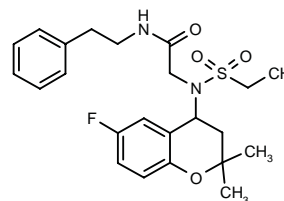
REFERENCES

1. Fung, M.S.C. et al. (Tanox, Inc.) *Inhibitors of complement activation*. WO 9942133.

ANTIARRHYTHMIC DRUGS

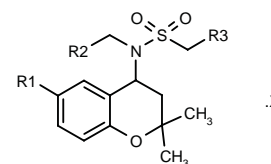
281164

2-[*N*-(Ethylsulfonyl)-*N*-(6-fluoro-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)amino]-*N*-(2-phenylethyl)-acetamide



C23 H29 F N2 O4 S; Mol wt: 448.5561

ACTION – Agent for the treatment or prevention of cardiovascular disorders, particularly arrhythmias, as well as gastrointestinal disorders such as ulcers, reflux esophagitis and diarrhea, a potassium channel blocker acting on cAMP-dependent potassium channels. Compound exhibited an IC₅₀ value of 0.046 µM for inhibition of human I_{Ks} channels expressed in *Xenopus* oocytes. Other compounds from this series of sulfonamide-substituted chroman derivatives include the following:



Compound	R1	R2	R3	X	Formula
281165	F	2-Pyr-NHCO	Me		C ₂₀ H ₂₄ FN ₃ O ₄ S
281166	OCH ₂ Ph	CH ₂ CH ₂ CON(Me)-CH ₂ CO ₂ Et	H		C ₂₈ H ₃₈ N ₂ O ₇ S
281167	OCH ₂ Ph	CON(Me)CH ₂ CO ₂ Et	H		C ₂₈ H ₃₄ N ₂ O ₇ S
281168	OCH ₂ Ph	CON(Me)CH ₂ CH ₂ Ph	H		C ₃₀ H ₃₆ N ₂ O ₅ S
281169	OCH ₂ Ph	2-Pyr-CH ₂ CH ₂ -N(Me)CO	H	HCl	C ₂₉ H ₃₅ N ₃ O ₅ S.HCl
281170	OBu	CH ₂ CH ₂ CH ₂ OMe	H		C ₂₁ H ₃₅ NO ₆ S
281171	F	CO ₂ CH ₂ CH ₂ -N(Me)CH ₂ Ph	Me		C ₂₅ H ₃₃ FN ₂ O ₅ S

SOURCE – Hoechst Marion Roussel (Aventis).

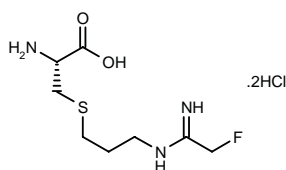
REFERENCES

1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulfonamide-substd. chromans, processes for their preparation, their use as a medicament or diagnostic, and pharmaceutical preparations comprising them*. DE 19742509, US 5955607.

MISCELLANEOUS CARDIOVASCULAR DRUGS

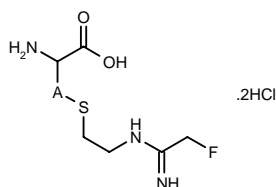
280973

S-[3-(2-Fluoro-1-iminoethylamino)propyl]-L-cysteine dihydrochloride



C₈ H₁₆ F N₃ O₂ S . 2HCl; Mol wt: 310.2192

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the inducible isoform of the enzyme (iNOS) over the constitutive isoforms; it is reported to have increased potency and a longer half-life *in vivo*. Other representative compounds from this series of halogenated amidino amino acid derivatives include the following:



Compound	A	Isomer	Formula
280974	-CH ₂ -	L	C ₇ H ₁₄ FN ₃ O ₂ S.2HCl
280975	-(CH ₂) ₂ -	DL	C ₈ H ₁₆ FN ₃ O ₂ S.2HCl
280976	-(CH ₂) ₂ -	L	C ₈ H ₁₆ FN ₃ O ₂ S.2HCl

SOURCE – Searle.

REFERENCES

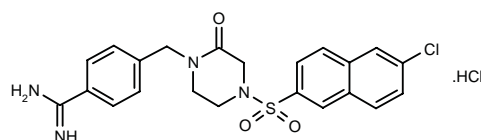
1. Hallinan, E.A. et al. (G.D. Searle & Co.) *Halogenated amidino amino acid derivs. useful as nitric oxide synthase inhibitors*. WO 9946240.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

280642

4-[4-(6-Chloronaphth-2-ylsulfonyl)-2-oxopiperazin-1-ylmethyl]benzamidinium hydrochloride



C₂₂ H₂₁ Cl N₄ O₃ S . HCl; Mol wt: 493.4128

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor (IC₅₀ = 0.050 μM). A representative compound from a series of sulfonamide derivatives.

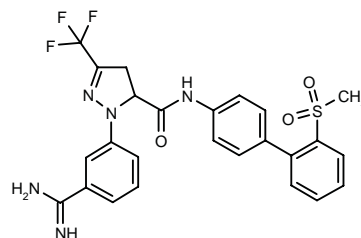
SOURCE – Takeda.

REFERENCES

1. Tawada, H. et al. (Takeda Chemical Industries, Ltd.) *Sulfonamide derivs., process for producing the same and utilization thereof*. WO 9940075.

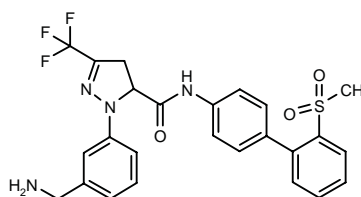
281538

1-(3-Amidinophenyl)-N-[2'-(methylsulfonyl)biphenyl-4-yl]-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-5-carboxamide



C₂₅ H₂₂ F₃ N₅ O₃ S; Mol wt: 529.5408

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, especially factor Xa. Another specifically claimed compound from this series of disubstituted pyrazolines and triazolines is:



281540: C₂₅ H₂₃ F₃ N₄ O₃ S

SOURCE – Hoechst Marion Roussel (Aventis).

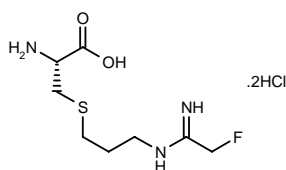
REFERENCES

1. Brendel, J. et al. (Hoechst Marion Roussel Deutschland GmbH) *Sulfonamide-substd. chromans, processes for their preparation, their use as a medicament or diagnostic, and pharmaceutical preparations comprising them*. DE 19742509, US 5955607.

MISCELLANEOUS CARDIOVASCULAR DRUGS

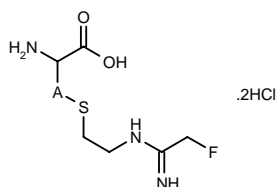
280973

S-[3-(2-Fluoro-1-iminoethylamino)propyl]-L-cysteine dihydrochloride



C₈ H₁₆ F N₃ O₂ S . 2HCl; Mol wt: 310.2192

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the inducible isoform of the enzyme (iNOS) over the constitutive isoforms; it is reported to have increased potency and a longer half-life *in vivo*. Other representative compounds from this series of halogenated amidino amino acid derivatives include the following:



Compound	A	Isomer	Formula
280974	-CH ₂ -	L	C ₇ H ₁₄ FN ₃ O ₂ S.2HCl
280975	-(CH ₂) ₂ -	DL	C ₈ H ₁₆ FN ₃ O ₂ S.2HCl
280976	-(CH ₂) ₂ -	L	C ₈ H ₁₆ FN ₃ O ₂ S.2HCl

SOURCE – Searle.

REFERENCES

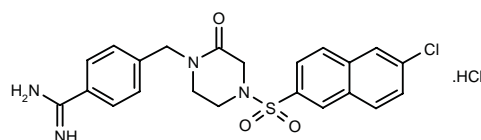
1. Hallinan, E.A. et al. (G.D. Searle & Co.) *Halogenated amidino amino acid derivs. useful as nitric oxide synthase inhibitors*. WO 9946240.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

280642

4-[4-(6-Chloronaphth-2-ylsulfonyl)-2-oxopiperazin-1-ylmethyl]benzamidinium hydrochloride



C₂₂ H₂₁ Cl N₄ O₃ S . HCl; Mol wt: 493.4128

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor (IC₅₀ = 0.050 μM). A representative compound from a series of sulfonamide derivatives.

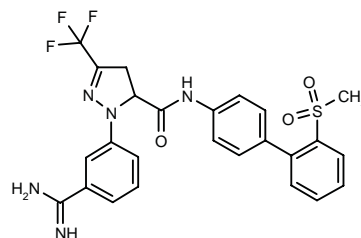
SOURCE – Takeda.

REFERENCES

1. Tawada, H. et al. (Takeda Chemical Industries, Ltd.) *Sulfonamide derivs., process for producing the same and utilization thereof*. WO 9940075.

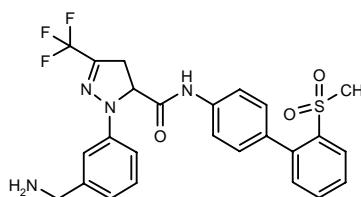
281538

1-(3-Amidinophenyl)-N-[2'-(methylsulfonyl)biphenyl-4-yl]-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-5-carboxamide



C₂₅ H₂₂ F₃ N₅ O₃ S; Mol wt: 529.5408

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, especially factor Xa. Another specifically claimed compound from this series of disubstituted pyrazolines and triazolines is:



281540: C₂₅ H₂₃ F₃ N₄ O₃ S

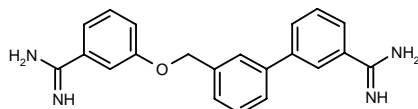
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Pinto, D.J.P. (DuPont Pharmaceuticals Co.) *Disubstd. pyrazolines and triazolines as factor Xa inhibitors*. WO 9950255.

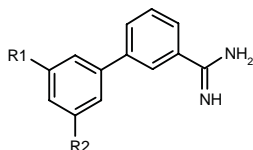
283094

3'-[3-(Amidino)phenoxyethyl]biphenyl-3-carboxamidine

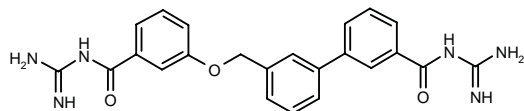


C21 H20 N4 O; Mol wt: 344.4160

ACTION – Factor Xa inhibitor potentially useful for the prophylaxis and/or treatment of thromboembolic disorders. Other specifically claimed biphenyl derivatives are:



Compound	R1	R2	Formula
283096	H	3-[NH2C(=NH)]-PhCH2O	C ₂₁ H ₂₀ N ₄ O
283097	CO2H	'3-[NH2C(=NH)]-PhOCH2	C ₂₂ H ₂₀ N ₄ O ₃
283099	OCH2CO2Me	4-[NH2C(=NH)]-PhOCH2	C ₂₄ H ₂₄ N ₄ O ₄
283100	OCH2CO2H	4-[NH2C(=NH)]-PhOCH2	C ₂₃ H ₂₂ N ₄ O ₄



283098: C23 H22 N6 O3

SOURCE – Merck KGaA.

REFERENCES

1. Gante, J. et al. (Merck Patent GmbH) *Biphenyl derivs*. DE 19819548, WO 9957096.

DERMATAN SULFATE⁺

135305

Dermatan 4-(hydrogen sulfate)

MF-701

ACTION – Naturally occurring glycosaminoglycan that potentiates the activity of heparin cofactor II, a physiologic specific thrombin inhibitor, while having no effect on the major heparin cofactor antithrombin III. It thus acts on the coagulation system as a selective thrombin inhibitor, unlike heparin.

INDICATION – Prevention of deep vein thrombosis.

PRESENTATION – Ampules (solution for injection), dermatan sulfate sodium salt, 100 mg/2 ml, 200 mg/2 ml and 300 mg/3 ml.

PROPRIETARY NAME – *Mistral* (IT).

SOURCES – Mediolanum; comarketed by Dompe.

RECENT REFERENCES

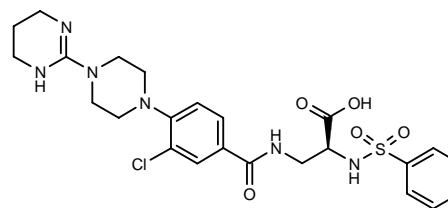
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6. Taliani, M.R. et al. *Dermatan sulphate in patients with heparin-induced thrombocytopenia*. Br J Haematol 1999, 104(1): 87.
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8. *New thrombin inhibitor approved in Italy for antithrombotic prophylaxis*. DailyDrugNews.com (Daily Essentials) 1999, July 29.

*Drug Data Rep 1991, 013(11): 0958.

ANTIPLATELET THERAPY

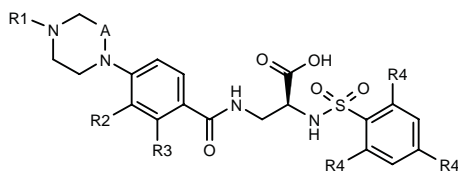
280396

3-[3-Chloro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)-piperazin-1-yl]benzamido]-2(S)-(phenylsulfonamido)-propionic acid



C24 H29 Cl N6 O5 S; Mol wt: 549.0491

ACTION – Dual vitronectin ($\alpha_v\beta_3$) and fibrinogen (gpIIb/IIIa) receptor antagonist (IC_{50} = 3.5 and < 0.2 nM, respectively) with much lower affinity for the fibronectin ($\alpha_5\beta_1$) receptor (IC_{50} = 63 μ M). Potentially useful for the treatment of acute ischemic diseases. Other exemplified compounds within this series of phenylpiperazine derivatives include the following



Compound	R1	R2	R3	R4	A	Formula
280397	3,4,5,6-tetrahydro-2-pyrimidinyl	NH2	Cl	H	-CH2-	C ₂₄ H ₃₀ ClN ₇ O ₅ S
280398	3,4,5,6-tetrahydro-2-pyrimidinyl	F	H	Me	-CH2-	C ₂₇ H ₃₅ FN ₆ O ₅ S
CP-4555 [280455]	2-benzimidazolyl	H	H	H	-CH2-	C ₂₇ H ₂₈ N ₆ O ₅ S
CP-4514 [280456]	3,4,5,6-tetrahydro-2-pyrimidinyl	H	H	H	-CH2-	C ₂₄ H ₃₀ N ₆ O ₅ S
280458	3,4,5,6-tetrahydro-2-pyrimidinyl	H	H	H	-(CH2)2-	C ₂₅ H ₃₂ N ₆ O ₅ S

SOURCE – Meiji Seika.

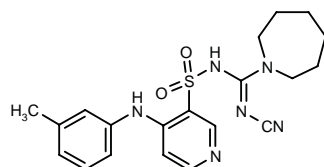
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BM-144¹⁻³

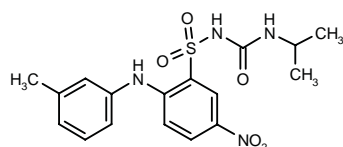
280644

N-[1-(Cyanoimino)-1-(perhydroazepin-1-yl)methyl]-4-(3-methylphenylamino)pyridine-3-sulfonamide



C₂₀ H₂₄ N₆ O₂ S; Mol wt: 412.5156

ACTION – Thromboxane A₂ (TxA₂) receptor antagonist (IC₅₀ = 0.12-0.28 μ M in washed human platelets), a torasemide derivative with the ability to inhibit both arachidonic acid- and U-46619-induced human platelet aggregation (IC₅₀ = 9.0-9.4 and 12.9-13.5 μ M, respectively) and to abolish the contractile effects of U-46619 on rat stomach strips and rat aorta (IC₅₀ = 0.81-1.01 and 0.12 μ M, respectively); it did not inhibit rat fundus contractions induced by PGE₂, PGF_{2 α} or PGI₂. Compound showed at least 10-fold greater TxA₂ receptor affinity than the parent compound and was generally more potent than the reference TxA₂ receptor antagonist sulotroban. At a dose of 30 mg/kg i.p., it prevented sudden death in rats (100% protection) induced by a lethal dose of U-46619 and, in contrast to torasemide, had no diuretic activity in rats at 30 mg/kg p.o. or i.p. Potentially useful for the treatment of thrombosis, asthma and hypertension. Another related torasemide derivative is:



BM-500 [280645]³: C₁₇ H₂₀ N₄ O₅ S

SOURCE – University of Liège, Liège (BE).

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1. Dogne, J.M. et al. *BM 144: An original thromboxane A₂ receptor antagonist derived from torasemide*. J Pharm Belg 1999, 54(2): 57.

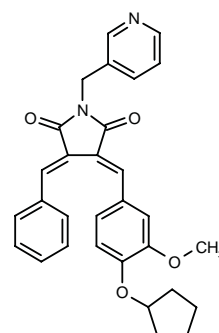
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3. Masereel, B. et al. *Thromboxane A₂ receptor antagonism in man and rat by a sulphonylurea (BM-144) and a sulphonylurea (BM-500)*. J Pharm Pharmacol 1999, 51(6): 695.

THROMBOLYTICS

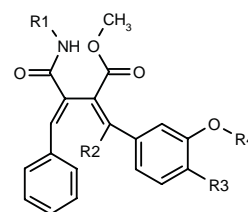
280515

3-[(*E*)-Benzylidene]-4-[(*E*)-4-(cyclopentyloxy)-3-methoxybenzylidene]-1-(3-pyridinylmethyl)pyrrolidine-2,5-dione

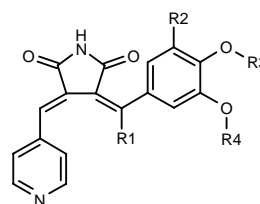


C₃₀ H₂₈ N₂ O₄; Mol wt: 480.5612

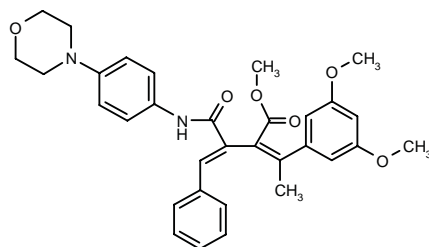
ACTION – Antithrombotic agent with potent plasminogen activator inhibitor type 1 (PAI-1)-inhibitory activity, as demonstrated by 100% inhibition of lipopolysaccharide-stimulated production of PAI-1 in bovine carotid artery endothelial cells at 1 μ M. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
280516	H	H	cyclopentyl-O	Me	C ₂₅ H ₂₇ N ₂ O ₅
280517	3-Pyr-CH2	Me	OMe	cyclopentyl	C ₃₂ H ₃₄ N ₂ O ₅



Compound	R1	R2	R3	R4	Formula
280518	H	H	cyclopentyl	Me	C ₂₃ H ₂₂ N ₂ O ₄
280519	Me	H	Me	cyclopentyl	C ₂₄ H ₂₄ N ₂ O ₄
280520	Me	OMe	Me	Me	C ₂₁ H ₂₀ N ₂ O ₅



280521: C₃₂ H₃₄ N₂ O₆

SOURCE – Tanabe Seiyaku.

REFERENCES

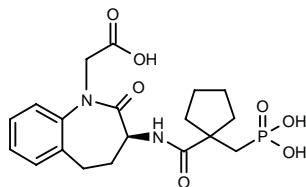
1. Ohmi, H. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 99189530.

RENAL-UROLOGIC DRUGS

DIURETICS

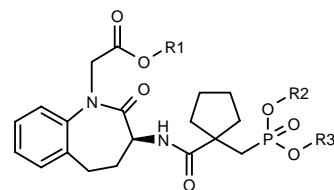
280844

2-[2-Oxo-3(*S*)-[1-(phosphonomethyl)cyclopentyl-carboxamido]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid



C₁₉ H₂₅ N₂ O₇ P; Mol wt: 424.3875

ACTION – Dual inhibitor of neutral endopeptidase (NEP; IC₅₀ = 1.7 nM) and endothelin-converting enzyme (ECE). Diuretic and natriuretic effects were demonstrated in rats at doses of 6.0 and 20.0 mg/kg i.v. (117 and 149% increase in urine volume, respectively, 147 and 246% increase in Na⁺ elimination, respectively, and 116 and 182% increase in K⁺ excretion, respectively). In addition, it showed significant antihypertensive activity in rats, where pretreatment with 10 mg/kg i.v. completely inhibited the pressor response to big endothelin in anesthetized rats. The minimum lethal dose in rats was > 215 mg/kg i.v. Potentially useful for the treatment of cardiac insufficiency. Other compounds from this series of (phosphonic acid-substituted 2-oxo-benzazepin-1-yl)acetic acid derivatives include the following:



Compound	R1	R2	R3	Formula
280845	t-Bu	CH(Me)CH ₂ Ph	H	C ₃₂ H ₄₃ N ₂ O ₇ P
280846	Et	H	H	C ₂₁ H ₂₉ N ₂ O ₇ P
280847	t-Bu	t-BuCOOCH ₂	Et	C ₃₁ H ₄₇ N ₂ O ₉ P
280848	t-Bu	H	H	C ₂₃ H ₃₃ N ₂ O ₇ P
280849	H	H	Et	C ₂₁ H ₂₉ N ₂ O ₇ P

SOURCE – Solvay.

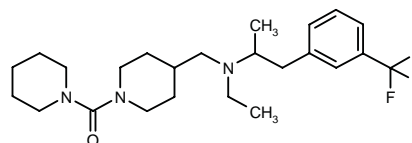
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1. Waldeck, H. et al. (Solvay Pharmaceuticals GmbH) *Phosphonic acid-substd. benzazepinone-N-acetic acid derivs. process for their preparation and pharmaceutical compsns. comprising them.* DE 19750002, JP 99292886, US 5952327.

TREATMENT OF URINARY INCONTINENCE

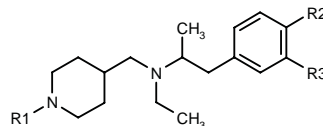
280800

1-[4-[*N*-Ethyl-*N*-[1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]aminomethyl]piperidin-1-yl]-1-(piperidin-1-yl)methanone

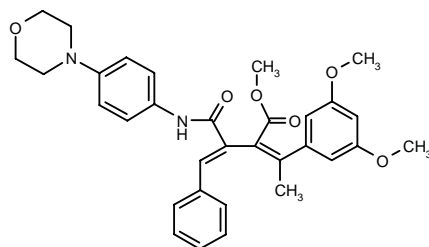


C₂₄ H₃₆ F₃ N₃ O; Mol wt: 439.5624

ACTION – Muscarinic receptor antagonist with potential in the treatment of genitourinary, gastrointestinal, respiratory, cardiovascular and CNS disorders, as well as for use in anesthesiology and ophthalmology. Other compounds from this series of *N*-(2-arylethyl)-*N*-(piperidin-4-ylmethyl)-amine derivatives include the following:



Compound	R1	R2	R3	Formula
280801	CON(Me) ₂	H	CF ₃	C ₂₁ H ₃₂ F ₃ N ₃ O
280802	1-Pip-CO	H	Cl	C ₂₃ H ₃₆ ClN ₃ O
280805	SO ₂ Me	-(CH ₂) ₃ -		C ₂₁ H ₃₄ N ₂ O ₂ S
280808	4-morpholinyl-CO	-C(Me) ₂ CH ₂ O-		C ₂₆ H ₄₁ N ₃ O ₃



280521: C₃₂ H₃₄ N₂ O₆

SOURCE – Tanabe Seiyaku.

REFERENCES

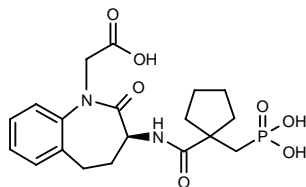
1. Ohmi, H. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns.* JP 99189530.

RENAL-UROLOGIC DRUGS

DIURETICS

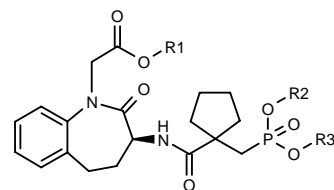
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280847	t-Bu	t-BuCOOCH ₂	Et	C ₃₁ H ₄₇ N ₂ O ₉ P
280848	t-Bu	H	H	C ₂₃ H ₃₃ N ₂ O ₇ P
280849	H	H	Et	C ₂₁ H ₂₉ N ₂ O ₇ P

SOURCE – Solvay.

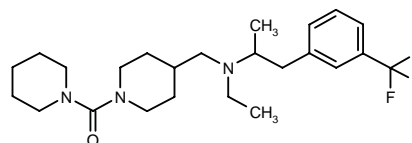
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TREATMENT OF URINARY INCONTINENCE

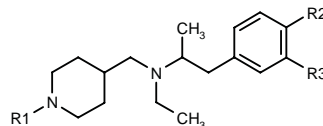
280800

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280805	SO ₂ Me	-(CH ₂) ₃ -		C ₂₁ H ₃₄ N ₂ O ₂ S
280808	4-morpholinyl-CO	-C(Me) ₂ CH ₂ O-		C ₂₆ H ₄₁ N ₃ O ₃

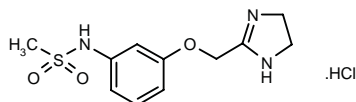
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REFERENCES

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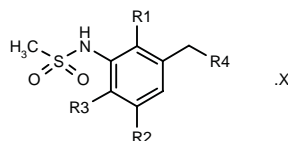
280866

N-[3-(4,5-Dihydro-1*H*-imidazol-2-ylmethoxy)phenyl]-methanesulfonamide hydrochloride



C11 H15 N3 O3 S . HCl; Mol wt: 305.7844

ACTION – Orally active, selective $\alpha_{1A/1L}$ -adrenoceptor agonist reported to increase lower urinary tract smooth muscle tone with little or no effect on the vasculature, heart or CNS. Claimed for the treatment of urinary incontinence, nasal congestion, priapism, depression, anxiety, dementia, senility, Alzheimer's disease, cognitive impairment and eating disorders. Other exemplified compounds from this series of 2-imidazoline, 2-oxazoline, 2-thiazoline and 4-imidazole derivatives include the following:



Compound	R1=R2	R3	R4	X	Formula
280867	Me	H	5-imidazolyl	oxalate	C ₁₃ H ₁₇ N ₃ O ₂ S.C ₂ H ₂ O ₄
280868	H	OMe	4,5-dihydro-2-imidazolyl	HCl	C ₁₂ H ₁₇ N ₃ O ₃ S.HCl

SOURCE – Roche Bioscience.

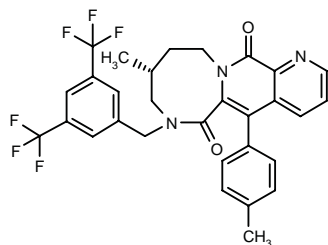
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1. Courmoyer, R.L. et al. (Syntex [USA], Inc.) *2-Imidazoline, 2-oxazoline, 2-thiazoline, and 4-imidazole derivs. of methylphenyl, methoxyphenyl, and aminophenyl alkylsulfonamides and ureas and their use*. US 5952362.

TAK-637

242974

(a*R*,9*R*)-7-[3,5-Bis(trifluoromethyl)benzyl]-9-methyl-5-(4-methylphenyl)-7,8,9,10,11,13-hexahydro-6*H*-[1,4]-diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione



C30 H25 F6 N3 O2; Mol wt: 573.5345

$[\alpha]_D^{20} +153.2^\circ$ (c 0.280, MeOH).

ACTION – Potent tachykinin NK₁ receptor antagonist (IC₅₀ = 0.45 nM for inhibition of [¹²⁵I]-BH-SP binding in human IM-9 cells) with high selectivity over rat NK₁ receptors (IC₅₀ = 85 nM in rat forebrain); it also showed potent and selective NK₁-antagonist effects in functional assays, with pA₂ values of 9.5 and 6.0 for NK₁ and NK₂ receptors, respectively, in guinea pig ileum, and it had little or no activity at NK₃ receptors (IC₅₀ > 1 μM for inhibition of [¹²⁵I]-Me-Phe-NKB binding in guinea pig cerebral cortex). Compound showed excellent activity *in vivo*, as demonstrated by inhibition of capsaicin-induced tracheal extravasation in guinea pigs (ID₅₀ = 4.3 and 33 mg/kg i.v. and p.o., respectively). It dose-dependently increased bladder capacity in anesthetized guinea pigs (ED₃₀ = 0.051 mg/kg i.v.) and in conscious guinea pigs (minimum effective dose [MED] = 0.01 mg/kg p.o.), without affecting voiding pressure; it showed no effect on either basal urethral pressure or phenylephrine-loaded urethral pressure. Chosen as a clinical candidate for the treatment of bladder function disorders.

SOURCE – Takeda.

REFERENCES

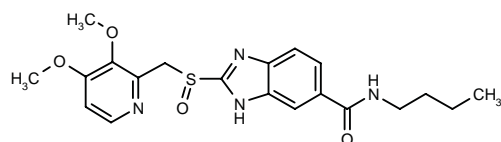
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4. Natsugari, H. et al. *Axially chiral 1,7-naphthyridine-6-carboxamide derivatives as orally active tachykinin NK1 receptor antagonists: Synthesis, antagonistic activity, and effects on bladder functions*. J Med Chem 1999, 42(19): 3982.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

279674

2-(3,4-Dimethoxyphenyl)-2-ylmethylsulfinyl)-*N*-butyl-1*H*-benzimidazole-6-carboxamide



C20 H24 N4 O4 S; Mol wt: 416.4996

ACTION – Antiulcer benzimidazole derivative proven to inhibit gastric H⁺/K⁺-ATPase and to exert gastric anti-secretory activity.

SOURCE – Shenyang Pharmaceutical University, Shenyang (CN).

REFERENCES

1. Huang, G.B. et al. *Studies on H⁺/K⁺-ATPase inhibitors benzimidazole derivatives*. Chin J Med Chem 1999, 9(2): 89.

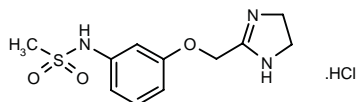
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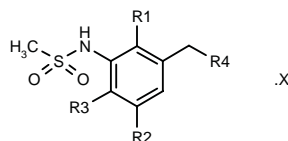
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SOURCE – Roche Bioscience.

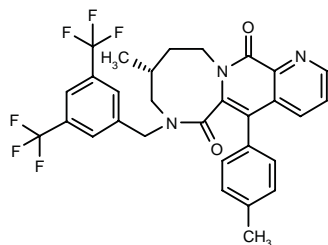
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TAK-637

242974

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C30 H25 F6 N3 O2; Mol wt: 573.5345

$[\alpha]_D^{20} +153.2^\circ$ (c 0.280, MeOH).

ACTION – Potent tachykinin NK₁ receptor antagonist (IC₅₀ = 0.45 nM for inhibition of [¹²⁵I]-BH-SP binding in human IM-9 cells) with high selectivity over rat NK₁ receptors (IC₅₀ = 85 nM in rat forebrain); it also showed potent and selective NK₁-antagonist effects in functional assays, with pA₂ values of 9.5 and 6.0 for NK₁ and NK₂ receptors, respectively, in guinea pig ileum, and it had little or no activity at NK₃ receptors (IC₅₀ > 1 μM for inhibition of [¹²⁵I]-Me-Phe-NKB binding in guinea pig cerebral cortex). Compound showed excellent activity *in vivo*, as demonstrated by inhibition of capsaicin-induced tracheal extravasation in guinea pigs (ID₅₀ = 4.3 and 33 mg/kg i.v. and p.o., respectively). It dose-dependently increased bladder capacity in anesthetized guinea pigs (ED₃₀ = 0.051 mg/kg i.v.) and in conscious guinea pigs (minimum effective dose [MED] = 0.01 mg/kg p.o.), without affecting voiding pressure; it showed no effect on either basal urethral pressure or phenylephrine-loaded urethral pressure. Chosen as a clinical candidate for the treatment of bladder function disorders.

SOURCE – Takeda.

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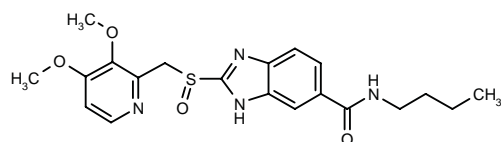
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2. Doi, T. et al. *Effects of TAK-637, a tachykinin receptor antagonist, on lower urinary tract function in the guinea pig*. Eur J Pharmacol 1999, 383(3): 297.
3. Kamo, I. et al. *Effects of TAK-637, and NK1 antagonist, on functions of lower urinary tract (1). A new pharmacotherapy for treatment of detrusor overactivity*. Jpn J Pharmacol 1999, 79(Suppl. I): Abst O-263.
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

279674

2-(3,4-Dimethoxyphenyl)-2-ylmethylsulfanyl)-*N*-butyl-1*H*-benzimidazole-6-carboxamide



C20 H24 N4 O4 S; Mol wt: 416.4996

ACTION – Antiulcer benzimidazole derivative proven to inhibit gastric H⁺/K⁺-ATPase and to exert gastric anti-secretory activity.

SOURCE – Shenyang Pharmaceutical University, Shenyang (CN).

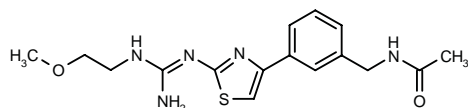
REFERENCES

1. Huang, G.B. et al. *Studies on H⁺/K⁺-ATPase inhibitors benzimidazole derivatives*. Chin J Med Chem 1999, 9(2): 89.

FR-145715

280554

N-[3-[2-[*N*³-(2-Methoxyethyl)guanidino]thiazol-4-yl]-benzyl]acetamide



C16 H21 N5 O2 S; Mol wt: 347.4409

ACTION – Antiulcer agent, a potent histamine H₂ receptor antagonist, as demonstrated in guinea pig atria by antagonism of histamine-induced positive chronotropic responses (IC₅₀ = 1.3 μM vs. = 3.3 μM for ranitidine). *In vivo*, compound was able to antagonize basal gastric acid secretion in conscious pylorus-ligated rats (ED₅₀ = 18.4 mg/kg i.d. vs. 30.5 mg/kg for ranitidine) and histamine-stimulated gastric acid secretion in anesthetized rats (ED₅₀ = 0.59 mg/kg i.v. vs. 0.10 mg/kg for ranitidine; ED₅₀ = 2.72 mg/kg i.d. vs. 0.17 mg/kg for ranitidine). In Heidenhain pouch dogs, compound inhibited tetragastrin-stimulated gastric acid secretion with ED₅₀ values of 0.12 and 0.32 mg/kg after i.v. or p.o. administration, respectively (ED₅₀ ranitidine = 0.08 mg/kg i.v., 0.33 mg/kg p.o.). Compound also showed gastroprotective activity in gastric lesion models in rats such as the water-immersion restraint stress- (ED₅₀ = 3.2 mg/kg p.o. vs. 1.5 mg/kg for ranitidine), acidified aspirin- (ED₅₀ = 15.1 mg/kg p.o. vs. no effect for ranitidine) and HCl-induced gastric lesions. In addition, it showed strong antibacterial activity against 10 strains of *Helicobacter pylori*, with a mean MIC of 0.32 μg/ml, and no effect against 25 other bacterial strains at up to 100 μg/ml. In gnotobiotic piglets infected with *H. pylori*, a dose of 16 mg/kg p.o. t.i.d. completely eliminated the microorganisms and reduced inflammation after 10 days of treatment.

SOURCE – Fujisawa.

REFERENCES

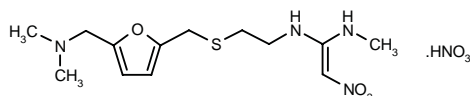
1. Katsura, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidino thiazoles and their use as H₂-receptor antagonist*. EP 545376, JP 94321921, US 5532258.
2. Ishikawa, H. et al. *FR145715, a novel histamine H₂ receptor antagonist, with specific anti-Helicobacter pylori activities*. Eur J Pharmacol 1999, 378(3): 299.

RANITIDINE NITRATE

Rec INNM

280901

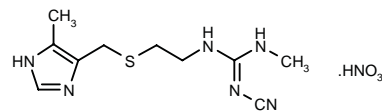
N-[2-[5-(Dimethylaminomethyl)furan-2-ylmethylsulfanyl]-ethyl]-*N*-methyl-2-nitrovinylidene-1,1-diamine nitrate



C13 H22 N4 O3 S . H N O3; Mol wt: 377.4197

ACTION – Nitrate salt of the known antiulcer agent ranitidine with improved gastroprotective properties, as demonstrated in a rat model of ethanol-induced gastric lesions, where 40% gastric damage was observed when administered at 62.5 mg/kg p.o. as compared to 80% damage with ranitidine administered at an equivalent dose

(50 mg/kg p.o.) and 100% damage with vehicle. No toxicity was observed following a single administration of 100 mg/kg p.o. to rats. Another exemplified compound from this series of nitrate salts of antiulcer agents is:



Cimetidine nitrate [280902]: C10 H16 N6 S . H N O3

SOURCE – NicOx.

REFERENCES

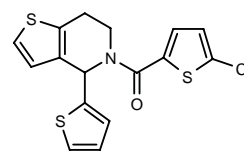
1. Del Soldato, P. (NicOx SA) *Nitrate salt of anti-ulcer medicine*. WO 9945004.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

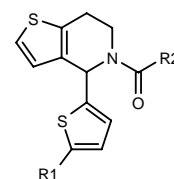
280903

1-(5-Chlorothiophen-2-yl)-1-[4-(2-thienyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]methanone



C16 H12 Cl N O S3; Mol wt: 365.9278

ACTION – Agent for the treatment or prevention of disorders of the endocrine system, particularly hyperglycemia and diabetes, and especially non-insulin-dependent diabetes mellitus (NIDDM), an inhibitor of glucose-6-phosphatases that acts as a normoglycemic agent. Other specifically claimed compounds from this series of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives include the following:

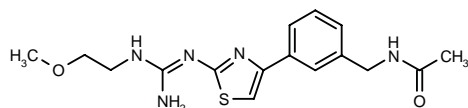


Compound	R1	R2	Formula
280904	H	4-(CH ₂ OH)-Ph	C ₁₉ H ₁₇ NO ₂ S ₂
280905	H	4-Cl-Ph	C ₁₈ H ₁₄ ClNO ₂ S ₂
280906	H	4-MeO-Ph	C ₁₉ H ₁₇ NO ₂ S ₂
280907	Cl	4-MeO-Ph	C ₁₉ H ₁₆ ClNO ₂ S ₂
280908	Cl	4-Cl-Ph	C ₁₈ H ₁₃ Cl ₂ NOS ₂
280909	Cl	4-MeO-cyclohexyl	C ₁₉ H ₂₂ ClNO ₂ S ₂
280910	Cl	1-Me-4-Pip	C ₁₈ H ₂₁ ClNO ₂ S ₂
280911	Cl	3-furyl-CH=CH	C ₁₈ H ₁₄ ClNO ₂ S ₂

FR-145715

280554

N-[3-[2-[*N*³-(2-Methoxyethyl)guanidino]thiazol-4-yl]-benzyl]acetamide



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ACTION – Antiulcer agent, a potent histamine H₂ receptor antagonist, as demonstrated in guinea pig atria by antagonism of histamine-induced positive chronotropic responses (IC₅₀ = 1.3 μM vs. = 3.3 μM for ranitidine). *In vivo*, compound was able to antagonize basal gastric acid secretion in conscious pylorus-ligated rats (ED₅₀ = 18.4 mg/kg i.d. vs. 30.5 mg/kg for ranitidine) and histamine-stimulated gastric acid secretion in anesthetized rats (ED₅₀ = 0.59 mg/kg i.v. vs. 0.10 mg/kg for ranitidine; ED₅₀ = 2.72 mg/kg i.d. vs. 0.17 mg/kg for ranitidine). In Heidenhain pouch dogs, compound inhibited tetragastrin-stimulated gastric acid secretion with ED₅₀ values of 0.12 and 0.32 mg/kg after i.v. or p.o. administration, respectively (ED₅₀ ranitidine = 0.08 mg/kg i.v., 0.33 mg/kg p.o.). Compound also showed gastroprotective activity in gastric lesion models in rats such as the water-immersion restraint stress- (ED₅₀ = 3.2 mg/kg p.o. vs. 1.5 mg/kg for ranitidine), acidified aspirin- (ED₅₀ = 15.1 mg/kg p.o. vs. no effect for ranitidine) and HCl-induced gastric lesions. In addition, it showed strong antibacterial activity against 10 strains of *Helicobacter pylori*, with a mean MIC of 0.32 μg/ml, and no effect against 25 other bacterial strains at up to 100 μg/ml. In gnotobiotic piglets infected with *H. pylori*, a dose of 16 mg/kg p.o. t.i.d. completely eliminated the microorganisms and reduced inflammation after 10 days of treatment.

SOURCE – Fujisawa.

REFERENCES

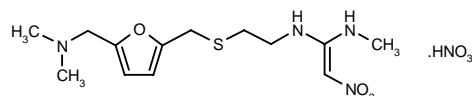
1. Katsura, Y. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidino thiazoles and their use as H₂-receptor antagonist*. EP 545376, JP 94321921, US 5532258.
2. Ishikawa, H. et al. *FR145715, a novel histamine H₂ receptor antagonist, with specific anti-Helicobacter pylori activities*. Eur J Pharmacol 1999, 378(3): 299.

RANITIDINE NITRATE

Rec INNM

280901

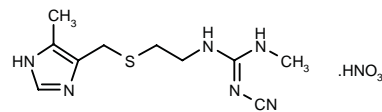
N-[2-[5-(Dimethylaminomethyl)furan-2-ylmethylsulfanyl]-ethyl]-*N*-methyl-2-nitrovinylidene-1,1-diamine nitrate



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ACTION – Nitrate salt of the known antiulcer agent ranitidine with improved gastroprotective properties, as demonstrated in a rat model of ethanol-induced gastric lesions, where 40% gastric damage was observed when administered at 62.5 mg/kg p.o. as compared to 80% damage with ranitidine administered at an equivalent dose

(50 mg/kg p.o.) and 100% damage with vehicle. No toxicity was observed following a single administration of 100 mg/kg p.o. to rats. Another exemplified compound from this series of nitrate salts of antiulcer agents is:



Cimetidine nitrate [280902]: C10 H16 N6 S . H N O3

SOURCE – NicOx.

REFERENCES

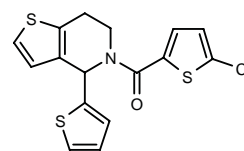
1. Del Soldato, P. (NicOx SA) *Nitrate salt of anti-ulcer medicine*. WO 9945004.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

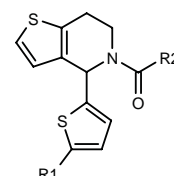
280903

1-(5-Chlorothiophen-2-yl)-1-[4-(2-thienyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]methanone



C16 H12 Cl N O S3; Mol wt: 365.9278

ACTION – Agent for the treatment or prevention of disorders of the endocrine system, particularly hyperglycemia and diabetes, and especially non-insulin-dependent diabetes mellitus (NIDDM), an inhibitor of glucose-6-phosphatases that acts as a normoglycemic agent. Other specifically claimed compounds from this series of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives include the following:



Compound	R1	R2	Formula
280904	H	4-(CH ₂ OH)-Ph	C ₁₉ H ₁₇ NO ₂ S ₂
280905	H	4-Cl-Ph	C ₁₈ H ₁₄ ClNOS ₂
280906	H	4-MeO-Ph	C ₁₉ H ₁₇ NO ₂ S ₂
280907	Cl	4-MeO-Ph	C ₁₉ H ₁₆ ClNO ₂ S ₂
280908	Cl	4-Cl-Ph	C ₁₈ H ₁₃ Cl ₂ NOS ₂
280909	Cl	4-MeO-cyclohexyl	C ₁₉ H ₂₂ ClNO ₂ S ₂
280910	Cl	1-Me-4-Pip	C ₁₈ H ₂₁ ClN ₂ OS ₂
280911	Cl	3-furyl-CH=CH	C ₁₈ H ₁₄ ClNO ₂ S ₂

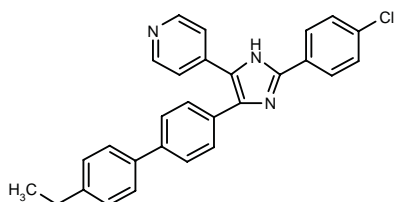
SOURCE – Novo Nordisk.

REFERENCES

1. Westergaard, N. et al. (Novo Nordisk A/S) 4,5,6,7-Tetrahydro-thieno[3,2-c]pyridine derivs. WO 9945013.

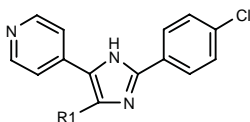
280937

4-[2-(4-Chlorophenyl)-4-(4'-ethylbiphenyl-4-yl)-1*H*-imidazol-5-yl]pyridine

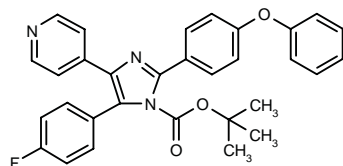


C28 H22 Cl N3; Mol wt: 435.9558

ACTION – Glucagon receptor antagonist that also inhibits the biosynthesis and/or action of cytokines such as TNF- α and IL-1. Potentially useful as an antidiabetic agent, as well as for the treatment of hypertension, cachexia and obesity. It may also be useful in the treatment of cytokine-mediated diseases such as rheumatoid arthritis, septic shock, inflammatory bowel disease, atherosclerosis, gout, adult respiratory distress syndrome, psoriasis, reperfusion injury and allograft rejection, among others. Other exemplified 2,4-diaryl-5-pyridyl imidazoles are:



Compound	R1	Formula
280939	COPh	C ₂₁ H ₁₄ ClN ₃ O
280940	4-(4-MeO-Ph)-Ph	C ₂₇ H ₂₀ ClN ₃ O



280938: C31 H26 F N3 O3

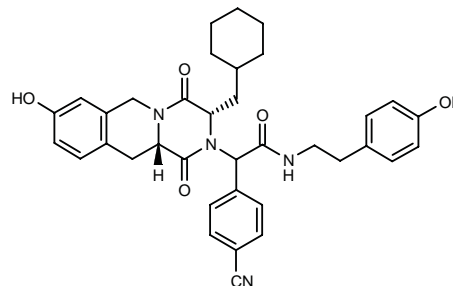
SOURCE – Merck & Co.

REFERENCES

1. Chang, L.L. (Merck & Co., Inc.) Triaryl subst. imidazoles, compsns. containing such cpds. and methods of use. US 5955480.

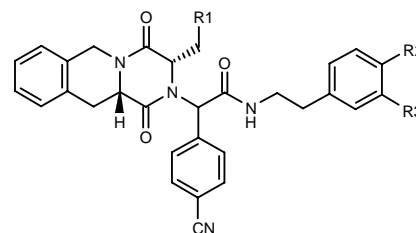
281309

2-(4-Cyanophenyl)-2-[3(*S*)-(cyclohexylmethyl)-1,4-dioxo-8-hydroxy-2,3,4,6,11,11a(*S*)-hexahydro-1*H*-pyrazino-[1,2-*b*]isoquinolin-2-yl]-*N*-[2-(4-hydroxyphenyl)ethyl]-acetamide



C36 H38 N4 O5; Mol wt: 606.7192

ACTION – Agent for the treatment of type II diabetes, an inhibitor of fructose-1,6-bisphosphatase (fructose-bisphosphatase; IC₅₀ = 0.37 μ M). Other compounds from this series of piperazine derivatives include the following:



Compound	R1	R2	R3	Formula
281310	cyclohexyl	OH	H	C ₃₆ H ₃₈ N ₄ O ₄
281311	cyclohexyl	H	OH	C ₃₆ H ₃₈ N ₄ O ₄
281312	Ph	OH	H	C ₃₆ H ₃₂ N ₄ O ₄

Fructose-bisphosphatase is a key rate-limiting enzyme in gluconeogenesis and inhibitors of FBPase are therefore predicted to reduce blood glucose levels via inhibition of gluconeogenesis.

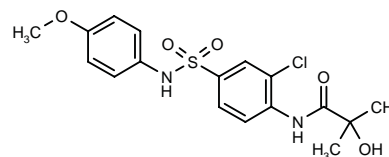
SOURCE – Ontogen.

REFERENCES

1. Mason, J.C. et al. (Ontogen Corp.) Piperazines as inhibitors of fructose-1,6-bisphosphatase (FBPase). WO 9947549.

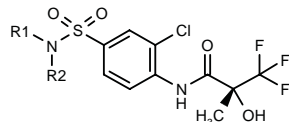
281339

N-[2-Chloro-4-[*N*-(4-methoxyphenyl)sulfamoyl]phenyl]-2-hydroxy-2-methylpropionamide



C17 H19 Cl N2 O5 S; Mol wt: 398.8651

ACTION – Agent for the treatment of diabetes mellitus, peripheral vascular disease, cardiac failure, myocardial ischemia, cerebral ischemia and reperfusion, muscle weakness, hyperlipidemia, Alzheimer's disease and atherosclerosis that acts by elevating pyruvate dehydrogenase (PDH) activity. Other preferred compounds from this series of benzenesulfonamide derivatives include the following:



Compound	R1	R2	Formula
281340	4-(AcNH)-Ph	H	C ₁₈ H ₁₇ ClF ₃ N ₃ O ₅ S
281341	4-(MeSO ₂)-Ph	H	C ₁₇ H ₁₆ ClF ₃ N ₂ O ₆ S ₂
281342	4-(NH ₂ SO ₂)-Ph	H	C ₁₆ H ₁₅ ClF ₃ N ₃ O ₆ S ₂
281343	4-(NH ₂ CO)-Ph	H	C ₁₇ H ₁₅ ClF ₃ N ₃ O ₅ S
281344	4-CN-Ph	H	C ₁₇ H ₁₃ ClF ₃ N ₃ O ₄ S
281345	4-Ac-Ph	H	C ₁₈ H ₁₆ ClF ₃ N ₂ O ₅ S
281346	-CH ₂ CH ₂ CH(OH)CH ₂ CH ₂ -		C ₁₅ H ₁₈ ClF ₃ N ₂ O ₅ S
281347	CH ₂ CH(OH)Me	H	C ₁₃ H ₁₆ ClF ₃ N ₂ O ₅ S
281348	2-pyrimidinyl	H	C ₁₄ H ₁₂ ClF ₃ N ₄ O ₄ S
281349	5-Me-2-Pyr	H	C ₁₆ H ₁₅ ClF ₃ N ₃ O ₄ S
281350	3-Pyr	H	C ₁₅ H ₁₃ ClF ₃ N ₃ O ₄ S
281351	4-OH-Ph	H	C ₁₆ H ₁₄ ClF ₃ N ₂ O ₅ S

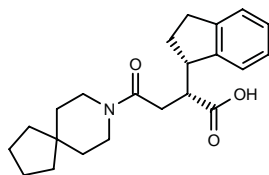
SOURCE – AstraZeneca.

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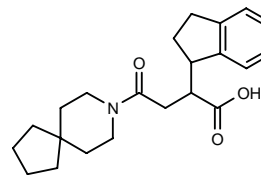
281878

4-(8-Azaspiro[4.5]dec-8-yl)-2(*R*)-[indan-1(*S*)-yl]-4-oxo-butyric acid



C₂₂ H₂₉ N O₃; Mol wt: 355.4751

ACTION – Hypoglycemic and antiinflammatory agent with blood glucose-lowering activity in rats and mice, and antiinflammatory activity in the carrageenan-induced paw edema model in rats. As such, it is expected to be useful in the treatment of diabetes, obesity and inflammation, i.e., diabetic neuropathy, polyarthritis, arthroses, etc. Other specifically claimed azacycloalkane derivatives are:



Compound	Isomer	Formula
281879	[2S(1R)]	C ₂₂ H ₂₉ NO ₃
281880	[2R(1R)]	C ₂₂ H ₂₉ NO ₃
281881	[2S(1S)]	C ₂₂ H ₂₉ NO ₃

SOURCE – Sanofi-Synthélabo.

REFERENCES

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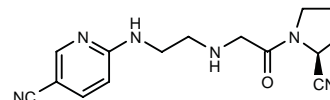
NVP-DPP-728

277256

6-[2-[2-[2(*S*)-Cyanopyrrolidinyl]-2-oxoethylamino]-ethylamino]pyridine-3-carbonitrile

1-[2-[2-(5-Cyano-2-pyridylamino)ethylamino]acetyl]-pyrrolidine-2(*S*)-carbonitrile

DPP-728



C₁₅ H₁₈ N₆ O; Mol wt: 298.3482

ACTION – Dipeptidyl peptidase IV (DPP-IV) inhibitor (IC₅₀ = 7 and 6 nM against human and rat DPP-IV, respectively) with > 15,000-fold selectivity over prolyl endopeptidase, DPP-II, trypsin and aminopeptidase P (IC₅₀ = 190, 110, > 300 and > 300 μM, respectively). In rats, compound given p.o. inhibited plasma DPP-IV with an ED₅₀ of 1 μmol/kg, and at a dose of 10 μmol/kg p.o. it increased the half-life of plasma glucagon-like peptide (GLP-1) and abolished the formation of the antagonistic metabolite (9-36) of GLP-1. Acute treatment with compound (10 μmol/kg i.v.) normalized glucose tolerance and β-cell responsiveness in dexamethasone-treated rats, a model of type II diabetes. In phase I clinical studies compound has been shown to inhibit DPP-IV and increase active GLP-1 levels in both healthy subjects and patients with type II diabetes, and to improve fasting and prandial glycemia in patients with type II diabetes; it is well tolerated at effective doses. It is presently undergoing phase II trials in type II diabetes.

SOURCE – Novartis.

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- Balkan, B. et al. *NVP-DPP728 improves β-cell function and glucose tolerance in dexamethasone-treated rats*. Diabetes 1999, 48(Suppl. 1): Abst 1192.
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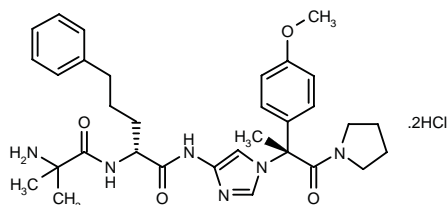
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

LY-444711

279804

2(*R*)-(2-Amino-2-methylpropanamido)-*N*-[1-[1(*R*)-(4-methoxyphenyl)-1-methyl-2-oxo-2-(1-pyrrolidinyl)ethyl]-1*H*-imidazol-4-yl]-5-phenylpentanamide dihydrochloride



C32 H42 N6 O4 . 2 HCl; Mol wt: 647.6436

ACTION – Highly potent and orally active growth hormone (GH) secretagogue ($EC_{50} = 1$ nM in rat pituitary cells) proven to stimulate GH secretion in dogs after oral administration (MED = 0.1 mg/kg) and to have good oral bioavailability (38%).

SOURCE – Lilly.

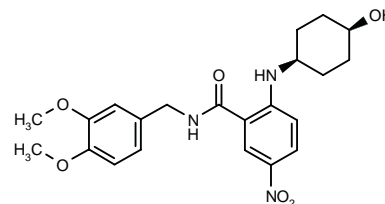
REFERENCES

- Dodge, J.A. et al. (Eli Lilly and Company) *Growth hormone secretagogues*. EP 933365, WO 9908699.
- Kauffman, R.F. and Palkowitz, A.D. (Eli Lilly and Company) *Treatment of congestive heart failure with growth hormone secretagogues*. WO 9908697.
- Dodge, J.A. et al. *Discovery of LY444711: A novel, highly potent, and orally active growth hormone secretagogue*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MED1 135.

TREATMENT OF MALE SEXUAL DYSFUNCTION

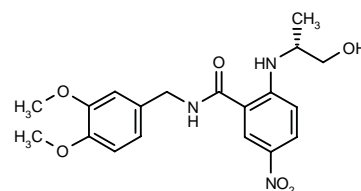
282379

cis-*N*-(3,4-Dimethoxybenzyl)-2-(4-hydroxycyclohexyl-amino)-5-nitrobenzamide



C22 H27 N3 O6; Mol wt: 429.4703

ACTION – cGMP-phosphodiesterase, especially PDE5, inhibitor with smooth muscle relaxant, bronchodilating, vasodilating, antiallergic and smooth muscle cell proliferation-inhibitory effects that is expected to be particularly useful for the treatment of erectile dysfunction or impotence. It was found to potentiate the relaxant response of rabbit corpora cavernosa to electrical field stimulation and prolonged the duration of detumescence following electrical stimulation in male dogs (mean prolongation of T75 was 52 s at 0.1 mg/kg i.v.), while being devoid of acute toxicity in mice following repeated oral doses of 32 mg/kg once a day for 14 consecutive days. Another preferred compound from this series of anthranilic acid derivatives is:



282381: C19 H23 N3 O6

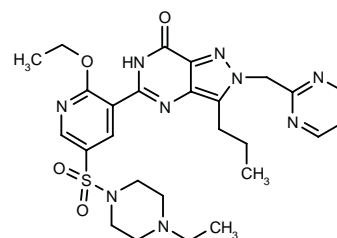
SOURCE – Fujisawa.

REFERENCES

- Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Anthranilic acid derivs. as inhibitors of the cGMP-phosphodiesterase*. WO 9954284.

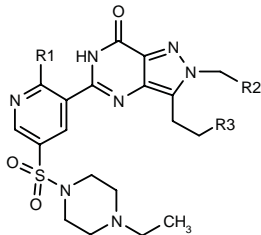
282478

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)pyridin-3-yl]-3-propyl-2-(2-pyrimidinylmethyl)-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

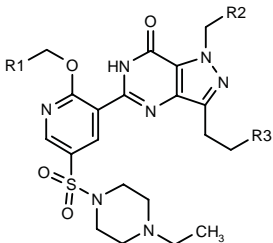


C26 H33 N9 O4 S; Mol wt: 567.6717

ACTION – Agent for the treatment of male erectile dysfunction and female sexual dysfunction, an inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 3.6 nM). Other representative compounds within this series of pyrazolo-pyrimidinones include the following:



Compound	R1	R2	R3	Formula
282479	OCH ₂ CH ₂ OEt	2-Pyr	Me	C ₂₉ H ₃₈ N ₈ O ₅ S
282480	O(CH ₂) ₃ OMe	2-Pyr	H	C ₂₈ H ₃₆ N ₈ O ₅ S
282481	3(R)-THF	2-Pyr	H	C ₂₈ H ₃₄ N ₈ O ₅ S
282484	(R,R)-OCH(Me)CH(Me)OMe	H	H	C ₂₄ H ₃₆ N ₇ O ₅ S
282485	2-Pyr-CH ₂ O	H	H	C ₂₅ H ₃₆ N ₈ O ₄ S
282487	1-pyrrolidinyl	2-Pyr	Me	C ₂₉ H ₃₇ N ₉ O ₅ S



Compound	R1	R2	R3	Formula
282482	CH ₂ OMe	1-Me-2-imidazolyl	H	C ₂₆ H ₃₅ N ₉ O ₅ S
282483	CH ₂ OMe	2-pyrimidinyl	Me	C ₂₇ H ₃₅ N ₉ O ₅ S
282486	2-Pyr	H	Me	C ₂₆ H ₃₂ N ₈ O ₄ S

SOURCE – Pfizer.

REFERENCES

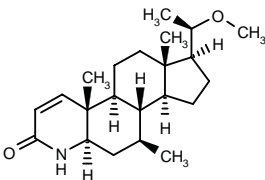
1. Bunnage, M.E. et al. (Pfizer Inc.;Pfizer Ltd.) *Pyrazolopyrimidinone cGMP PDE5 inhibitors for the treatment of sexual dysfunction*. WO 9954333.

DERMATOLOGIC DRUGS

ACNE THERAPY

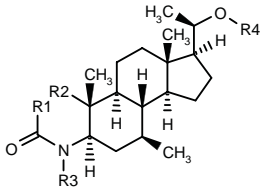
279793

20(S)-Methoxy-7β-methyl-4-aza-5α-pregn-1-en-3-one



C22 H35 N O2; Mol wt: 345.5235

ACTION – Potent and selective human steroid 5α-reductase type 1 inhibitor (IC₅₀ = 1.8 nM) with about 3000-fold selectivity over type 2 enzyme (IC₅₀ = 5375 nM); compound did not act on other common steroid-binding enzymes nor on the human androgen receptor. It showed a good pharmacokinetic profile in both rats and rhesus monkeys. Potentially useful for the treatment of androgen-related skin conditions such as acne, and as combination therapy with a type 2-selective inhibitor such as finasteride for complete suppression of dihydrotestosterone in the treatment of benign prostatic hyperplasia, hirsutism and male pattern baldness. Other representative compounds within this series 3-oxo-4aza-5α-7β-methylpregnan-20-ethers include the following:



Compound	R1	R2	R3	R4	Formula
279794	-CH=CH-		H	3-Cl-Ph	C ₂₇ H ₃₆ ClNO ₂
279795	-(CH ₂) ₂ -		Me	3-Pyr	C ₂₇ H ₄₀ N ₂ O ₂

SOURCE – Merck & Co.

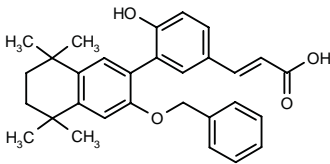
REFERENCES

1. Bakshi, R.K. et al. *3-Oxo-4aza-5α-7β-methylpregnan-20-ethers as inhibitors of human type 1 5α-reductase: Synthesis and structure-activity relationship*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst 226.

281448

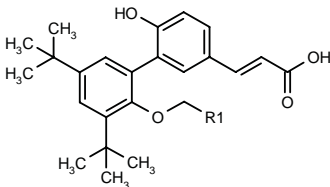
3-[3-(3-Benzyloxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-hydroxyphenyl]acrylic acid

3-[3-(3-Benzyloxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-hydroxyphenyl]prop-2(E)-enoic acid



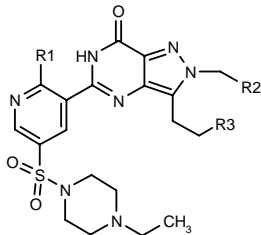
C30 H32 O4; Mol wt: 456.5788

ACTION – Agent for the treatment of skin disorders including acne, ichthyoses and other keratinization and hyperproliferative disorders with retinoid X receptor (RXR)-antagonist activity (K_D = 14 nM). Other aromatic bicyclic compounds include the following:

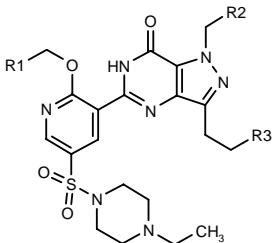


Compound	R1	Formula
281449	Ph	C ₃₀ H ₃₄ O ₄
281450	Bu	C ₂₈ H ₃₈ O ₄

ACTION – Agent for the treatment of male erectile dysfunction and female sexual dysfunction, an inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 3.6 nM). Other representative compounds within this series of pyrazolo-pyrimidinones include the following:



Compound	R1	R2	R3	Formula
282479	OCH2CH2OEt	2-Pyr	Me	C ₂₉ H ₃₈ N ₈ O ₅ S
282480	O(CH2)3OMe	2-Pyr	H	C ₂₈ H ₃₆ N ₈ O ₅ S
282481	3(R)-THF	2-Pyr	H	C ₂₈ H ₃₄ N ₈ O ₅ S
282484	(R,R)-OCH(Me)CH(Me)OMe	H	H	C ₂₄ H ₃₆ N ₇ O ₅ S
282485	2-Pyr-CH2O	H	H	C ₂₅ H ₃₆ N ₈ O ₄ S
282487	1-pyrrolidinyl	2-Pyr	Me	C ₂₉ H ₃₇ N ₉ O ₅ S



Compound	R1	R2	R3	Formula
282482	CH2OMe	1-Me-2-imidazolyl	H	C ₂₆ H ₃₅ N ₉ O ₅ S
282483	CH2OMe	2-pyrimidinyl	Me	C ₂₇ H ₃₅ N ₉ O ₅ S
282486	2-Pyr	H	Me	C ₂₆ H ₃₂ N ₈ O ₄ S

SOURCE – Pfizer.

REFERENCES

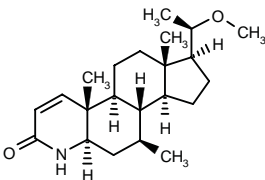
1. Bunnage, M.E. et al. (Pfizer Inc.;Pfizer Ltd.) *Pyrazolopyrimidinone cGMP PDE5 inhibitors for the treatment of sexual dysfunction*. WO 9954333.

DERMATOLOGIC DRUGS

ACNE THERAPY

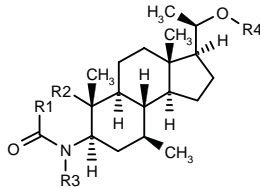
279793

20(S)-Methoxy-7β-methyl-4-aza-5α-pregn-1-en-3-one



C22 H35 N O2; Mol wt: 345.5235

ACTION – Potent and selective human steroid 5α-reductase type 1 inhibitor (IC₅₀ = 1.8 nM) with about 3000-fold selectivity over type 2 enzyme (IC₅₀ = 5375 nM); compound did not act on other common steroid-binding enzymes nor on the human androgen receptor. It showed a good pharmacokinetic profile in both rats and rhesus monkeys. Potentially useful for the treatment of androgen-related skin conditions such as acne, and as combination therapy with a type 2-selective inhibitor such as finasteride for complete suppression of dihydrotestosterone in the treatment of benign prostatic hyperplasia, hirsutism and male pattern baldness. Other representative compounds within this series 3-oxo-4aza-5α-7β-methylpregnan-20-ethers include the following:



Compound	R1	R2	R3	R4	Formula
279794	-CH=CH-		H	3-Cl-Ph	C ₂₇ H ₃₆ ClNO ₂
279795	-(CH2)2-		Me	3-Pyr	C ₂₇ H ₄₀ N ₂ O ₂

SOURCE – Merck & Co.

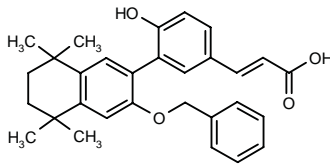
REFERENCES

1. Bakshi, R.K. et al. *3-Oxo-4aza-5α-7β-methylpregnan-20-ethers as inhibitors of human type 1 5α-reductase: Synthesis and structure-activity relationship*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst 226.

281448

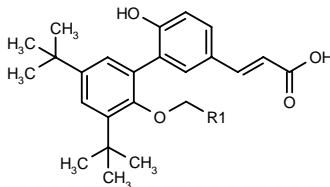
3-[3-(3-Benzyloxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-hydroxyphenyl]acrylic acid

3-[3-(3-Benzyloxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-hydroxyphenyl]prop-2(E)-enoic acid



C30 H32 O4; Mol wt: 456.5788

ACTION – Agent for the treatment of skin disorders including acne, ichthyoses and other keratinization and hyperproliferative disorders with retinoid X receptor (RXR)-antagonist activity (K_D = 14 nM). Other aromatic bicyclic compounds include the following:



Compound	R1	Formula
281449	Ph	C ₃₀ H ₃₄ O ₄
281450	Bu	C ₂₈ H ₃₈ O ₄

SOURCE – Galderma.

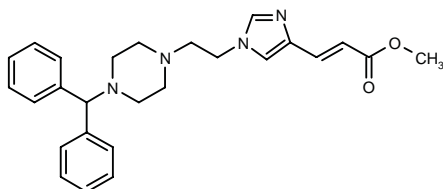
REFERENCES

1. Bernardon, J.-M. (CIRD Galderma) *Bicyclic aromatic cpds. and their use in human and veterinary medicine as well as in cosmetology*. CA 2264979, EP 947496, FR 2776657.

TREATMENT FOR ALLERGIC SKIN DISORDERS

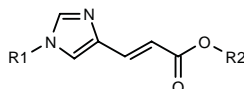
280659

3-[1-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl]-1*H*-imidazol-4-yl]prop-2(*E*)-enoic acid methyl ester



C26 H30 N4 O2; Mol wt: 430.5490

ACTION – Antiallergic agent whose activity was demonstrated in the rat passive cutaneous anaphylaxis (PCA) reaction (28.7% inhibition at 100 mg/kg p.o.) and in a murine model of DNFB-induced contact dermatitis (73.5 and 47.8% inhibition when given as a 0.2% topical solution or 100 mg/kg p.o., respectively). Other compounds from this series of urocanic acid derivatives include the following:



Compound	R1	R2	Formula
280660	4-CO2Et-Ph	Me	C ₁₆ H ₁₆ N ₂ O ₄
280661	4-[(Ph) ₂ CH]-1-Piz-CH ₂ CH ₂	H	C ₂₅ H ₂₈ N ₄ O ₂
280662	4-[2-Pyr-CH(Ph)]-1-Piz-CH ₂ CH ₂	Me	C ₂₅ H ₂₉ N ₅ O ₂
280663	4-NH ₂ -Ph	Me	C ₁₃ H ₁₃ N ₃ O ₂
280664	4-[(Ph) ₂ CH]-1-Piz-CH ₂ CH ₂	Et	C ₂₇ H ₃₂ N ₄ O ₂

SOURCE – Senju.

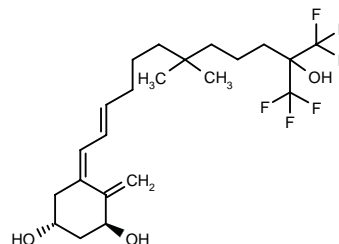
REFERENCES

1. Ogata, K. et al. (Senju Pharmaceuticals Co., Ltd.) *Urocanic acid derivs*. WO 9940071.

ANTIPSORIATICS

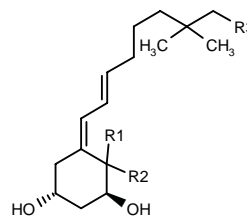
280746

4-Methylene-5(*Z*)-[12,12,12-trifluoro-11-hydroxy-7,7-dimethyl-11-(trifluoromethyl)dodec-2(*E*)-enylidene]-1(*R*),3(*S*)-cyclohexanediol



C22 H32 F6 O3; Mol wt: 458.4798

ACTION – Retiferol derivative with potential in the treatment of hyperproliferative skin diseases such as psoriasis, basal cell carcinomas, disorders of keratinization and keratosis and for reversing conditions associated with photodamage. Compound exhibited comparable activity to calcitriol in a vitamin D receptor (VDR) activation assay in COS cells transfected with the human VDR (EC₅₀ = 4 nM vs. 2.8 nM for calcitriol), while showing much lower calcemic potential in mice, where it exhibited a highest tolerated dose (HTD) for no weight loss of 80 µg/kg when administered s.c. daily for 4 days, compared to 0.5 µg/kg for calcitriol. When tested in hairless mice, it promoted epidermal thickening with an ED₅₀ of 200 µg/kg p.o. and showed an HTD of 80 µg/kg p.o., while calcitriol exhibited ED₅₀ and HTD values of 500 and 1 µg/kg p.o., respectively; compound thus shows a 200-fold improved therapeutic index as compared to calcitriol. Similar improved results as compared to calcitriol were obtained when compound was tested in minipigs for epidermal proliferation-promoting activity. A representative compound from a series of cyclohexanediol derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
280747	H	H	(<i>Z</i>)-CH=CHC(CF ₃) ₂ OH	C ₂₁ H ₃₀ F ₆ O ₃
280748	-CH ₂ -		(<i>Z</i>)-CH=CHC(CF ₃) ₂ OH	C ₂₂ H ₃₀ F ₆ O ₃
280749	-CH ₂ -		(<i>E</i>)-CH=CHC(CF ₃) ₂ OH	C ₂₁ H ₃₀ F ₆ O ₃
280751	H	H	(<i>E</i>)-CH=CHC(CF ₃) ₂ OH	C ₂₁ H ₃₀ F ₆ O ₃
280754	H	H	CH ₂ CH ₂ C(CF ₃) ₂ OH	C ₂₁ H ₃₂ F ₆ O ₃
280755	-CH ₂ -		CH ₂ CH ₂ C(Me) ₂ OH	C ₂₂ H ₃₈ O ₃
280756	H	H	CH ₂ CH ₂ C(Me) ₂ OH	C ₂₁ H ₃₈ O ₃
280758	H	H	ethynylene-C(CF ₃) ₂ OH	C ₂₁ H ₂₈ F ₆ O ₃
280759	-CH ₂ -		ethynylene-C(CF ₃) ₂ OH	C ₂₂ H ₂₈ F ₆ O ₃
280760	H	H	ethynylene-C(Me) ₂ OH	C ₂₁ H ₃₄ O ₃

SOURCE – Roche.

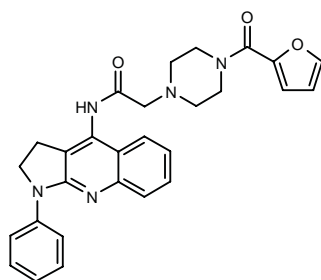
REFERENCES

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OTHER DERMATOLOGIC DRUGS

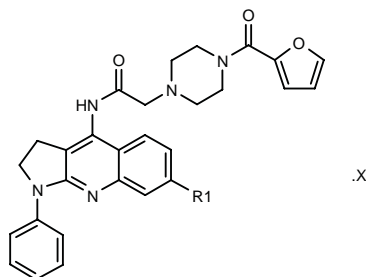
280408

2-[4-(2-Furylcarbonyl)piperazin-1-yl]-*N*-(1-phenyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4-yl)acetamide



C₂₈ H₂₇ N₅ O₃; Mol wt: 481.5533

ACTION – Agent for the treatment of inflammation, cancer and ischemia–reperfusion disorders, an inhibitor of E-selectin (IC₅₀ = 250 μM), P-selectin (IC₅₀ = 76 μM) and L-selectin (IC₅₀ = 72 μM) binding. It inhibited cell infiltration in a murine model of antigen-induced ear inflammation by 37% at a dose of 10 mg/kg i.v. Other exemplified compounds from this series of furoyl-substituted piperazine derivatives include the following:



Compound	R1	X	Formula
280409	H	HCl	C ₂₈ H ₂₇ N ₅ O ₃ ·HCl
280410	H	MeSO ₃ H	C ₂₈ H ₂₇ N ₅ O ₃ ·CH ₄ O ₃ S
280411	Me		C ₂₉ H ₂₉ N ₅ O ₃

SOURCE – Kanebo (Nippon Organon).

REFERENCES

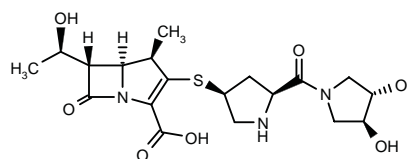
1. Kiyoi, T. et al. (Kanebo, Ltd.) *1-Furyl substd. piperadine derivs., drug containing them as effective ingredient, and intermediates for producing them.* JP 99180980.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

280089

(1*R*,5*S*,6*S*)-2-[5(*S*)-[3(*S*),4(*S*)-Dihydroxypyrrolidin-1-ylcarbonyl]pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C₁₉ H₂₇ N₃ O₇ S; Mol wt: 441.5023

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against Gram-positive and Gram-negative pathogens including *Staphylococcus aureus* SG 511 (MIC = 0.098 μg/ml), *Streptococcus pyogenes* (MIC = 0.007 μg/ml), *Escherichia coli* strains 078 and 1507E (MIC = 0.013 and 0.025 μg/ml, respectively), *Enterococcus faecium* MD 8B (MIC = 6.25 μg/ml), *Enterococcus cloacae* 1321E (MIC = 0.13 μg/ml) and *Pseudomonas aeruginosa* strains 1592E and 1771M (MIC = 0.195 and 0.098 μg/ml, respectively). In comparison with meropenem, it showed similar *in vitro* antibacterial activity and slightly less stability to DHP-I (renal dehydropeptidase I). In mice, compound showed a favorable pharmacokinetic profile with good oral bioavailability, and excellent therapeutic efficacy in systemic infections induced by *E. coli*, *S. pyogenes* and *P. aeruginosa* (PD₅₀ = 0.94, 4.79 and 3.93 mg/kg s.c., respectively); it was approximately 5-fold more effective than meropenem against systemic infections induced by *S. aureus* (PD₅₀ = 2.18 and 11.1 mg/kg s.c., respectively).

SOURCES – Korea Institute of Science & Technology, Seoul (KR); Korea Research Institute of Chemical Technology, Taejon (KR).

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1. Kang, Y.K. et al. *Synthesis and biological evaluation of novel 1β-methylcarbapenems having a new moiety at C-2.* Bioorg Med Chem Lett 1999, 9(16): 2385.

SOURCE – Roche.

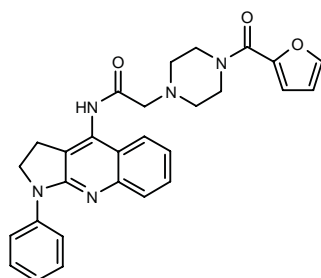
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1. Barbier, P. et al. (F. Hoffmann-La Roche AG) *Cyclohexanediol derivs.* WO 9943646.

OTHER DERMATOLOGIC DRUGS

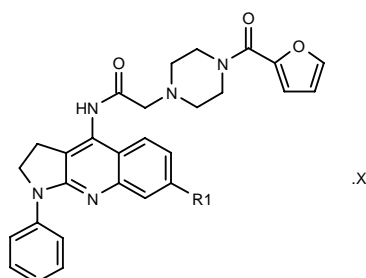
280408

2-[4-(2-Furylcarbonyl)piperazin-1-yl]-*N*-(1-phenyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4-yl)acetamide



C₂₈ H₂₇ N₅ O₃; Mol wt: 481.5533

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Compound	R1	X	Formula
280409	H	HCl	C ₂₈ H ₂₇ N ₅ O ₃ ·HCl
280410	H	MeSO ₃ H	C ₂₈ H ₂₇ N ₅ O ₃ ·CH ₄ O ₃ S
280411	Me		C ₂₉ H ₂₉ N ₅ O ₃

SOURCE – Kanebo (Nippon Organon).

REFERENCES

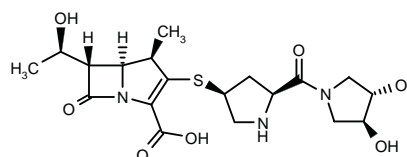
1. Kiyoi, T. et al. (Kanebo, Ltd.) *1-Furyl substd. piperadine derivs., drug containing them as effective ingredient, and intermediates for producing them.* JP 99180980.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

280089

(1*R*,5*S*,6*S*)-2-[5(*S*)-[3(*S*),4(*S*)-Dihydroxypyrrolidin-1-ylcarbonyl]pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C₁₉ H₂₇ N₃ O₇ S; Mol wt: 441.5023

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against Gram-positive and Gram-negative pathogens including *Staphylococcus aureus* SG 511 (MIC = 0.098 μg/ml), *Streptococcus pyogenes* (MIC = 0.007 μg/ml), *Escherichia coli* strains 078 and 1507E (MIC = 0.013 and 0.025 μg/ml, respectively), *Enterococcus faecium* MD 8B (MIC = 6.25 μg/ml), *Enterococcus cloacae* 1321E (MIC = 0.13 μg/ml) and *Pseudomonas aeruginosa* strains 1592E and 1771M (MIC = 0.195 and 0.098 μg/ml, respectively). In comparison with meropenem, it showed similar *in vitro* antibacterial activity and slightly less stability to DHP-I (renal dehydropeptidase I). In mice, compound showed a favorable pharmacokinetic profile with good oral bioavailability, and excellent therapeutic efficacy in systemic infections induced by *E. coli*, *S. pyogenes* and *P. aeruginosa* (PD₅₀ = 0.94, 4.79 and 3.93 mg/kg s.c., respectively); it was approximately 5-fold more effective than meropenem against systemic infections induced by *S. aureus* (PD₅₀ = 2.18 and 11.1 mg/kg s.c., respectively).

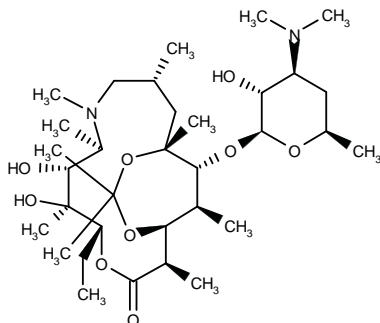
SOURCES – Korea Institute of Science & Technology, Seoul (KR); Korea Research Institute of Chemical Technology, Taejon (KR).

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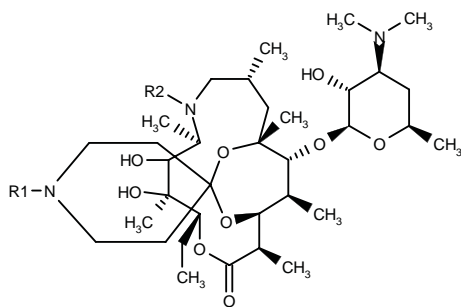
281155

9a-Aza-3-des(hexopyranosyl)-9-desoxo-3-*O*,6-*O*-isopropylidene-9a-homoerythromycin A

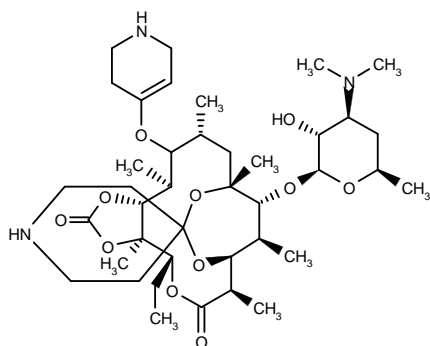


C33 H62 N2 O9; Mol wt: 630.8578

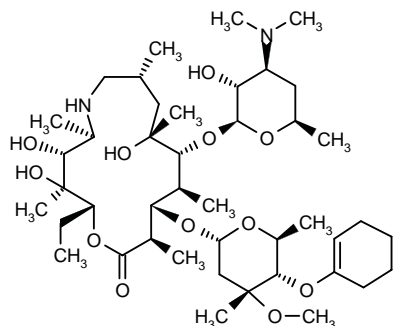
ACTION – Agent for the treatment of bacterial, parasitic and protozoal infections, a representative compound from a series of 3,6-ketal and enol ether macrolide antibiotics, wherein the following are also included:



Compound	R1	R2	Formula
281156	cyclohexyl-NHCO	Me	C ₄₂ H ₇₆ N ₄ O ₁₀
281158	SO ₂ CH ₂ CO ₂ Me	Me	C ₃₈ H ₆₉ N ₃ O ₁₃ S
281160	2-thienyl-CH ₂ CO	H	C ₄₀ H ₆₇ N ₃ O ₁₀ S
281161	COCH ₂ N(Me)CH ₂ Ph	Me	C ₄₅ H ₇₈ N ₄ O ₁₀
281162	4-oxo-4H-1-benzopyran-2-yl-CO	Me	C ₄₅ H ₆₉ N ₃ O ₁₂
281163	3-CF ₃ -4-(PhCH ₂ OCO)-Ph	H	C ₄₉ H ₇₂ F ₃ N ₃ O ₁₁



281157: C40 H67 N3 O11



281159: C43 H78 N2 O12

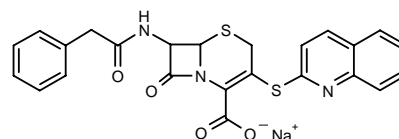
SOURCE – Pfizer.

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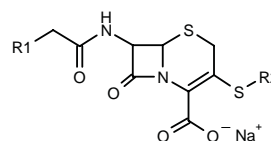
282893

7-(2-Phenylacetamido)-3-(2-quinolinylsulfanyl)-3-cephem-4-carboxylic acid sodium salt



C24 H18 N3 Na O4 S2; Mol wt: 499.5452

ACTION – Cephem antibiotic proven to have good activity against methicillin-susceptible and -resistant *Staphylococcus aureus*, giving MIC values of < 0.05 µg/ml against strain FDA 209P and 3.13 µg/ml against strain F-579. Other exemplified cephalosporin derivatives include the following:



Compound	R1	R2	Formula
282894	4-MeO-Ph	4-NH ₂ -1H-pyrazolo-[3,4-d]pyrimidin-6-yl	C ₂₁ H ₁₈ N ₇ NaO ₅ S ₂
282895	3-MeO-Ph	4-NH ₂ -1H-pyrazolo-[3,4-d]pyrimidin-6-yl	C ₂₁ H ₁₈ N ₇ NaO ₅ S ₂
282896	1,3,4-thiadiazol-2-yl-S	4-NH ₂ -1H-pyrazolo-[3,4-d]pyrimidin-6-yl	C ₁₆ H ₁₂ N ₉ NaO ₄ S ₄
282897	Ph	9H-purin-6-yl	C ₂₀ H ₁₅ N ₆ NaO ₄ S ₂
282898	Ph	9-NH ₂ -9H-purin-6-yl	C ₂₀ H ₁₆ N ₇ NaO ₄ S ₂
282899	Ph	pyrazolo[3,4-d]-pyrimidin-4-yl	C ₂₀ H ₁₅ N ₆ NaO ₄ S ₂
282900	Ph	7-OH-pyrido-[2,3-d]pyrimidin-2-yl	C ₂₂ H ₁₆ N ₅ NaO ₅ S ₂

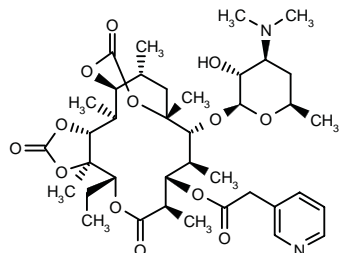
SOURCE – Toyama.

REFERENCES

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FMA-122***264392**

3-Des(hexopyranosyl)-9-deoxo-9(*S*)-hydroxy-3-*O*-[2-(3-pyridyl)acetyl]erythromycin A 6-*O*,9-*O*:11-*O*,12-*O*-bis-(cyclic carbonate)



C38 H56 N2 O13; Mol wt: 748.8614

ACTION – Macrolide (acylide) antibiotic with broad-spectrum activity against Gram-positive and Gram-negative bacteria and superior activity to azithromycin against *Haemophilus influenzae*, erythromycin-sensitive *Staphylococcus aureus* and erythromycin-susceptible *Streptococcus pneumoniae* (MIC = 0.78, 0.10 and 0.025 µg/ml, respectively, vs. 1.56, 0.39 and 0.10 µg/ml, respectively, for azithromycin), as well as against erythromycin-resistant *S. pneumoniae* (MIC = 0.1-6.25 µg/ml for compound vs. 0.78- > 100 µg/ml for azithromycin). *In vivo*, compound (0.3-3 mg/kg p.o.) protected mice from experimental systemic *S. pneumoniae* infections with efficacy comparable to azithromycin.

SOURCE – Taisho.

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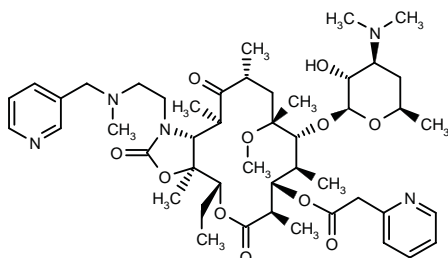
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*Identified compound **264392** Drug Data Rep 1998, 020(08): 0696.

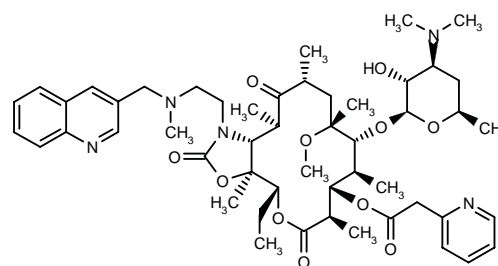
FMA-199**280984**

11-Deoxy-3-des(cladinosyl)-11-[2-[*N*-methyl-*N*-(3-pyridylmethyl)amino]ethylamino]-3-*O*-(2-pyridylacetyl)-6-*O*-methylerythromycin A 11-*N*,12-*O*-cyclic carbamate



C47 H71 N5 O11; Mol wt: 882.1019

ACTION – Macrolide antibiotic with excellent activity against erythromycin-resistant *Streptococcus pneumoniae* (MIC = 0.39 and 1.56 µg/ml against *S. pneumoniae* 205 and *S. pneumoniae* 211, respectively), as well as against erythromycin-susceptible *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Bordetella pertussis* and *Helicobacter pylori* (MIC = 0.10, 3.13, < 0.025, 0.05, 0.10, < 0.025 and 0.05 µg/ml, respectively). In mice with systemic infections caused by *S. pneumoniae*, compound given orally at a dose of 2 mg/mouse or s.c. at a dose of 0.2 mg/mouse for 7 days provided complete protection (100% survival rate), being more effective than clarithromycin. A favorable pharmacokinetic profile was observed after oral administration in mice, with high C_{max} values (4.79 µg/ml) and a long $t_{1/2}$ (2.93 h). Another related acylide is:



FMA-481 [280985]: C51 H73 N5 O11

SOURCE – Taisho.

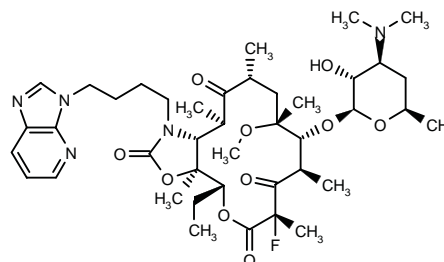
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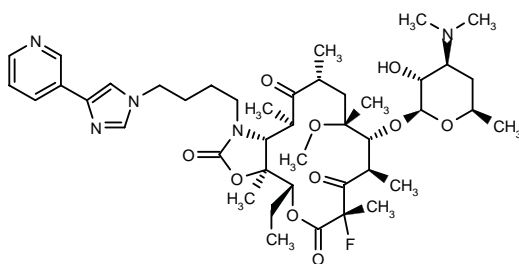
HMR-3787*1,3-5,7,8**256335**

11-Deoxy-3-des(hexopyranosyloxy)-2-fluoro-11-[4-(3*H*-imidazo[4,5-*b*]pyridin-3-yl)butylamino]-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate



C41 H62 F N5 O10; Mol wt: 803.9638

ACTION – Ketolide antibiotic with broad-spectrum activity against Gram-positive respiratory tract pathogens such as staphylococci, streptococci, pneumococci, *Haemophilus influenza* and *Moraxella catarrhalis* and including erythromycin-resistant strains and penicillin- or macrolide-resistant strains ($MIC_{90} = 0.01$ -1.2 mg/l), with the exception of constitutively MLS_B resistant strains of *Staphylococcus aureus*; it was also active against enterococci ($MIC_{90} = 0.005$ -5 mg/l). *In vivo* studies in murine infection models showed high therapeutic efficacy for compound, PD_{50} values ranging from < 1.5 to 29.4 mg/kg p.o. against infections caused by erythromycin-susceptible and -resistant strains of *S. aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Enterococcus faecalis*; it was somewhat less effective against ampicillin-susceptible or -resistant *H. influenzae* infections ($PD_{50} = 54$ -64 mg/kg p.o.), but more so than clarithromycin or azithromycin. Another related ketolide is:



HMR-3562 [280977]¹⁻⁸: C43 H64 F N5 O10

SOURCE – Hoechst Marion Roussel (Aventis).

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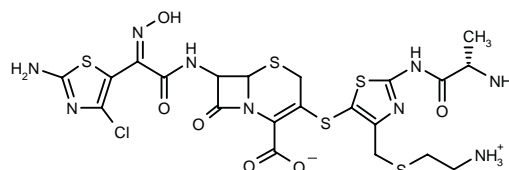
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*Identified compound **256335** Drug Data Rep 1998, 020(01): 0057.

MC-03,971

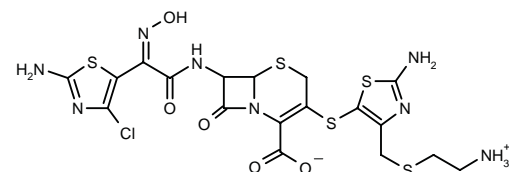
280718

3-[2-(L-Alanyl-amino)-4-(2-aminoethylsulfanylmethyl)-thiazol-5-ylsulfany]-7-[2-(2-amino-4-chlorothiazol-5-yl)-2-(hydroxyimino)acetamido]-3-cephem-4-carboxylic acid inner salt



C21 H24 Cl N9 O6 S5; Mol wt: 694.2606

ACTION – Cephem antibiotic, the *N*-alanyl prodrug of **MC-03,791** with an improved water solubility and pharmacokinetic profile. MC-03,791 displayed high antibacterial activity against β -lactam-resistant Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA; $MIC_{90} = 2$ μ g/ml). In mice, compound showed good efficacy against septicemia caused by both methicillin-sensitive *S. aureus* and MRSA ($ED_{50} = 0.2$ and 2.5 mg/kg s.c., respectively).



MC-03,791 [280717]: C18 H19 Cl N8 O5 S5

SOURCE – Microcide.

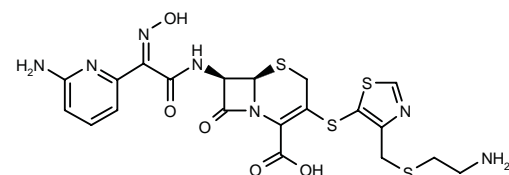
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MC-03,260

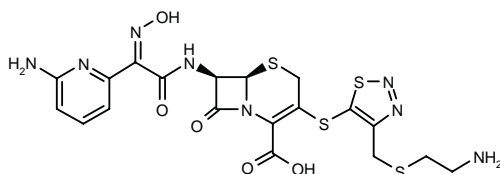
280721

(6*R*,7*R*)-3-[4-(2-Aminoethylsulfanylmethyl)thiazol-5-ylsulfany]-7-[2-(6-aminopyridin-2-yl)-2-(hydroxyimino)acetamido]-3-cephem-4-carboxylic acid



C20 H21 N7 O5 S4; Mol wt: 567.6939

ACTION – Cephalosporin antibiotic active against sensitive and resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 1-2 µg/ml) and methicillin-sensitive *S. aureus* (MIC = 0.125 µg/ml). Compound showed excellent water solubility (> 20 mg/ml at pH 4.5) and was able to protect against mortality caused by *S. aureus* Smith in a mouse sepsis model (ED₅₀ = 0.4 mg/kg s.c.). Another related dibasic cephalosporin is:



MC-02,867 [280719]: C₁₉ H₂₀ N₈ O₅ S₄

SOURCE – Microcide.

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SYNERCID®

166760

Defined mixture of pure and synergistic mesilate salts of quinupristin and dalbapristin in a ratio 30/70 in %, w:w

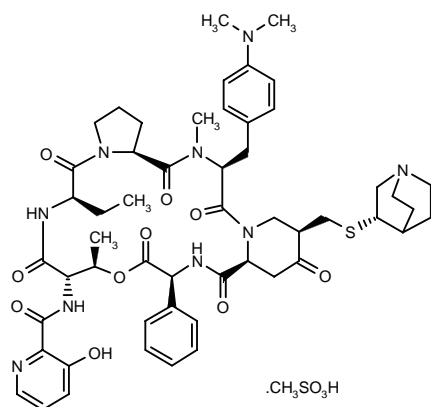
RP-59500+
RPR-59500

Quinupristin mesilate

Rec INNM; USAN

138965

N-(3-Hydroxy-2-pyridylcarbonyl)-(*S*)-threonyl-(*R*)-(α -aminobutyryl)-(*S*)-prolyl-[*N*-methyl-4-(dimethylamino)]-(*S*)-phenylalanyl-[4-oxo-5(*R*)-[quinuclidin-3(*S*)-ylthiomethyl]-(*S*)-homopropyl]-(*S*)-phenylglycine C-1.6-O-3.1-lactone methanesulfonate



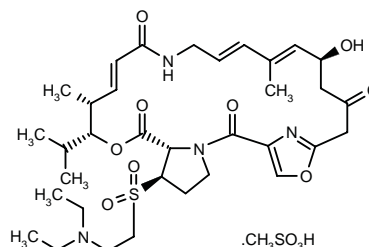
C53 H67 N9 O10 S . C H4 O3 S ; Mol wt: 1118.3370

Dalbapristin mesilate

Rec INNM

166761

(26a*S*)-26(*R*)-[2-(Dimethylamino)ethylsulfonyl]-14(*S*)-hydroxy-3(*R*)-isopropyl-4(*R*),12-dimethyl-3,4,8,9,14,15,16,17,24,25,26,26a-dodecahydro-1*H*,7*H*,22*H*-21,18-nitrilopyrrolo[2,1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22-tetraone methanesulfonate



C34 H50 N4 O9 S . C H4 O3 S ; Mol wt: 786.9596

ACTION – Streptogramin antibiotic.

INDICATION – Treatment of infections known or suspected to be caused by susceptible Gram-positive microorganisms, when i.v. therapy is appropriate and when there are no other antibacterial agents active against the organisms: nosocomial pneumonia, skin and soft tissue infections and clinically significant infections due to *Enterococcus faecium*.

PRESENTATION – Single-dose vials containing powder for solution for infusion, 150 mg quinupristin mesilate and 350 mg dalbapristin mesilate salt.

PROPRIETARY NAME – Synercid (GB).

SOURCE – Rhône-Poulenc Rorer (Aventis).

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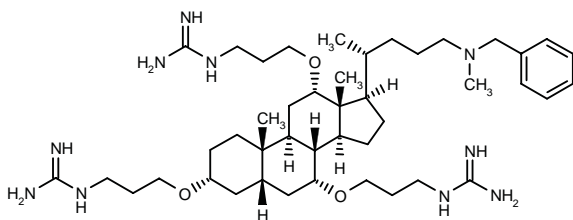
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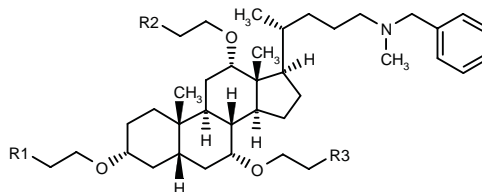
280953

24-(*N*-Benzyl-*N*-methylamino)-3 α ,7 α ,12 α -tris(3-guanidinopropoxy)-5 β -cholane



C44 H78 N10 O3; Mol wt: 795.1672

ACTION – Antibacterial agent that acts as a bacteriostatic and bactericidal agent by binding to the outer cellular membrane of bacteria; it also acts to sensitize bacteria to other antibiotics by increasing the permeability of the outer membrane of the bacteria. *In vitro*, it exhibited MIC and MBC values of 2 and 4, 2 and 4, and 6 and 15 μ g/ml, respectively, against *Escherichia coli* ATCC 10798 and 25922 strains and *Pseudomonas aeruginosa* ATCC 27853. When tested against *E. coli* ATCC 10798 in combination with erythromycin, it reduced the MIC value of the latter from 70 μ g/ml to 1 μ g/ml at a concentration of 1 μ g/ml; sensitization to novobiocin was also observed, the MIC value decreasing from > 500 μ g/ml to 1 μ g/ml when combined with test compound at 2 μ g/ml. Similar results were observed against the other two strains. A representative compound from a series of steroid-derived antibiotics, wherein the following are also included:



Compound	R1=R2=R3	Formula
280954	NHC(=NH)NH2	C ₄₁ H ₇₂ N ₁₀ O ₃
280955	NH2	C ₃₈ H ₆₆ N ₄ O ₃
280956	CH2NH2	C ₄₁ H ₇₂ N ₄ O ₃

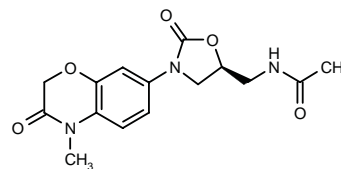
SOURCE – Brigham Young University, Provo, UT (US).

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280997

N-[3-(4-Methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C15 H17 N3 O5; Mol wt: 319.3153

ACTION – Oxazolidinone antibacterial agent with potent *in vitro* activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (MIC = 1-2 μ g/ml), as well as *Haemophilus influenzae* (MIC = 8 μ g/ml), with an antibacterial profile comparable to linezolid. *In vivo*, compound at 25 mg/kg s.c. at 1 and 5 h postinfection protected against *S. aureus*-induced systemic infection in mice with better activity than linezolid, and it showed more favorable pharmacokinetic properties following single i.v. doses in mice.

SOURCE – Bayer.

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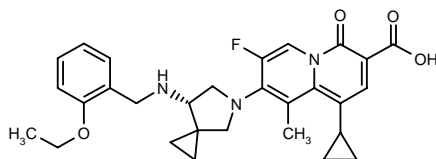
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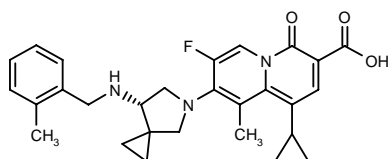
280735

1-Cyclopropyl-8-[7(S)-(2-ethoxybenzylamino)-5-aza-spiro[2.4]hept-5-yl]-7-fluoro-9-methyl-4-oxo-4H-quinoline-3-carboxylic acid



C29 H32 F N3 O4; Mol wt: 505.5868

ACTION – Fluoro-2-pyridone antibacterial agent with broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC = 0.01-0.39 µg/ml), *Enterococcus faecium*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aeruginosa* (MIC = 0.2, 1.1, 0.1 and 1.56 µg/ml, respectively); in comparison to ciprofloxacin and trovafloxacin, compound showed similar antibacterial activity but an improved safety profile in a human topoisomerase II assay and a clonogenic cytotoxicity assay (IC₅₀ > 100 µg/ml). Within this class of fluoro-2-pyridones, the following is also described:



A-272117 [280734]: C28 H30 F N3 O3

SOURCE – Abbott.

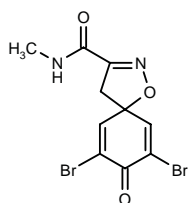
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KY-9

276273

7,9-Dibromo-N-methyl-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide



C10 H8 Br2 N2 O3; Mol wt: 363.9922

ACTION – Antibacterial agent extracted from marine biomaterial with bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) including vancomycin-resistant strains (MIC = 3.15-6.25 µg/ml). Compound acts by the inhibiting the formation of penicillin-binding protein PBP2' and showed synergistic activity in combination with arbekacin.

SOURCES – Keio University, Tokyo (JP); Sankyo.

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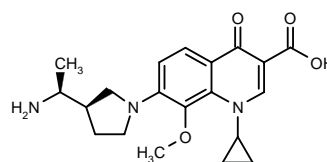
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PGE-9262932

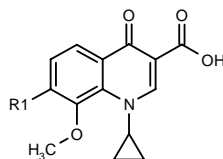
280988

7-[3(R)-[1(S)-Aminoethyl]pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C20 H25 N3 O4; Mol wt: 371.4345

ACTION – Nonfluoroquinolone (NFQ) antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative pathogens including quinolone-resistant *Streptococcus pneumoniae*, penicillin-resistant *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA), being more active against Gram-positive microorganisms than fluoroquinolones such as ciprofloxacin, trovafloxacin, levofloxacin and gatifloxacin; it showed rapid bactericidal activity against MRSA. Compound displayed potent inhibition of both molecular targets (DNA gyrase and topoisomerase IV) and may thus be associated with a reduced potential for the development of resistance in *S. aureus*. *In vivo*, it exhibited good protection against lethal murine infections caused by Gram-positive, Gram-negative and drug-resistant bacteria following both s.c. and p.o. administration. Compound also showed favorable preliminary toxicological and pharmacokinetic profiles. Other related NFQs are:



Compound	R1	Formula
PGE-4175997 [275618]*	(R)-3-[C(Me)2NH2]-1-pyrrolidinyl	C ₂₁ H ₂₇ N ₃ O ₄
PGE-9509924 [280989]	(S)-3-NH2-1-Pip	C ₁₉ H ₂₃ N ₃ O ₄
PGE-510629 [280990]	3(R)-[(S)-MeNHCH(Me)]-1-pyrrolidinyl	C ₂₁ H ₂₇ N ₃ O ₄

SOURCE – Procter & Gamble.

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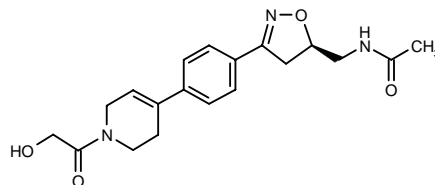
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- Bierman, J. et al. *In vivo efficacy of a series of nonfluoroquinolones (NFQs) in mice*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F551.
- Brown, S.D. et al. *In vitro antibacterial activity of a series of novel nonfluoroquinolones (NFQs) against bacterial pathogens*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F549.
- Gazda, M. et al. *Preformulation characterization of a series of novel nonfluoroquinolones (NFQs)*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F552.
- Hannah-Hardy, J. et al. *Acute IV toxicity and clastogenicity of novel, 8-methoxy-nonfluoroquinolones compared with 8-methyl-fluoroquinolones*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F553.
- Ledoussal, B. et al. *Novel nonfluoroquinolones (NFQs), structure-activity, and design of new potent and safe agents*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F544.
- Mallalieu, N.L. et al. *Preclinical pharmacokinetics of a series of nonfluoroquinolones (NFQs)*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F550.
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- Roychoudhury, S. et al. *In vitro antibacterial activity of a series of nonfluoroquinolones (NFQs) against penicillin- and quinolone-resistant strains of Streptococcus pneumoniae*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F548.
- Roychoudhury, S. et al. *In vitro antibacterial activity of a series of nonfluoroquinolones (NFQs) against quinolone-resistant isolates of methicillin-resistant Staphylococcus aureus (MRSA)*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F547.
- Roychoudhury, S. et al. *Whole-cell inhibition of dual molecular targets by a series of nonfluoroquinolones (NFQs) in Staphylococcus aureus*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F546.
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*Identified compound **275618** (see **275617**) Drug Data Rep 1999, 021(06): 0526.

PNU-171832*

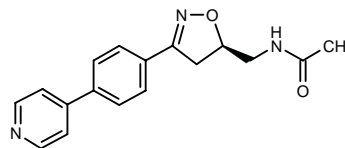
263298

N-[3-[4-[1-(2-Hydroxyacetyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl]-4,5-dihydroisoxazol-5(*R*)-ylmethyl]acetamide



C₁₉ H₂₃ N₃ O₄; Mol wt: 357.4077

ACTION – Phenylisoxazolidinone antibacterial agent with *in vitro* activity and *in vivo* efficacy comparable to linezolid. Another related compound is:



PNU-173954 [264004]**: C₁₇ H₁₇ N₃ O₂

SOURCE – Pharmacia & Upjohn.

REFERENCES

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- Barbachyn, M.R. et al. *Oxazolidinone bioisosteres: Studies leading to the identification of phenylisoxazolines as novel and potent antibacterial agents*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F572.

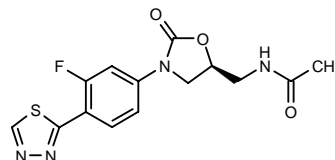
*Identified compound **263298** Drug Data Rep 1998, 020(06): 0520.

Identified compound **264004 (see **263298**) Drug Data Rep 1998, 020(06): 0520.

PNU-176665

280991

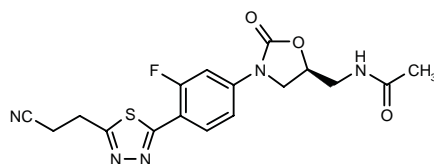
N-[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-oxazolidin-5(*S*)-ylmethyl]acetamide



C₁₄ H₁₃ F N₄ O₃ S; Mol wt: 336.3457

ACTION – Oxazolidinone antibacterial agent active against Gram-positive bacteria including methicillin-sensitive *Staphylococcus aureus* UC9213, methicillin-resistant *S. aureus* UC12673, penicillin-sensitive *Streptococcus pneumoniae* UC9912 and methicillin-resistant *Staphylococcus epidermidis* UC12084 (MIC = 1, 1, 0.25 and 0.25 µg/ml, respectively), as well as against vancomycin-sensitive *Enterococcus faecalis* UC9217 (MIC = 1 µg/ml); compound also exhibited unusually good activity against fastidious Gram-negative organisms such as *Haemophilus influenzae* 30063 and *Moraxella*

catarrhalis 30607 (MIC = 4 µg/ml). Compound demonstrated good *in vivo* activity in a mouse model of bacteremia induced by *S. aureus* UC9213 (ED₅₀ = 2.2 mg/kg p.o.). Within this series of azolyphenyl oxazolidinones, the following is also included:



280992: C17 H16 F N5 O3 S

SOURCE – Pharmacia & Upjohn.

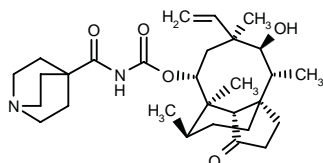
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SB-247386²⁻⁴

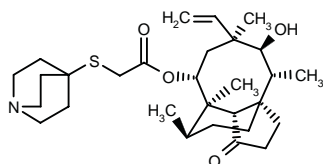
280854

(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*S*,10*R*)-*N*-(Quinuclidin-4-ylcarbonyl)carbamic acid 5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinyldecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester



C29 H44 N2 O5; Mol wt: 500.6756

ACTION – Antibacterial agent, a semisynthetic pleuromutilin with good antibacterial activity against Gram-positive microorganisms commonly associated with skin and skin structure and respiratory tract infections. In particular, compound exhibited potent antibacterial activity against clinical isolates with known resistance to common antimicrobial agents including methicillin-sensitive, methicillin-resistant, mupirocin-resistant and fusidic acid-resistant *Staphylococcus aureus* (MIC₅₀ = 0.5, 2, 1 and 0.25 µg/ml, respectively), penicillin-sensitive and -resistant *Streptococcus pneumoniae* (MIC = 0.25 µg/ml), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, coagulase-negative staphylococci, *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 1, 0.06, 0.25, 1 and 0.25 µg/ml, respectively). In contrast to mupirocin, significant resistance to compound did not develop in *S. aureus*. *In vivo*, it demonstrated exceptional efficacy, superior to mupirocin, against topical infections caused by two strains of *S. aureus*. Another compound within this class of pleuromutilins is:



SB-268091 [276524]^{*,1,3,4}: C29 H45 N O4 S2

SOURCE – SmithKline Beecham.

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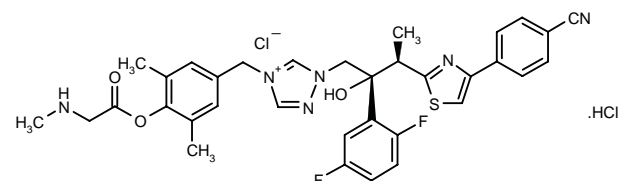
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*Identified compound **276524** Drug Data Rep 1999, 021(07): 0627.

ANTIFUNGAL AGENTS

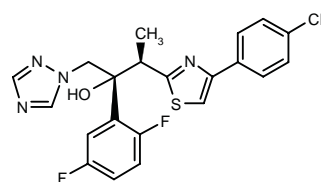
281149

1-[3(*R*)-[4-(4-Cyanophenyl)thiazol-2-yl]-2(*R*)-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[2-(methylamino)acetoxy]benzyl]-1*H*-1,2,4-triazol-4-ium chloride hydrochloride



C34 H33 Cl F2 N6 O3 S . HCl; Mol wt: 715.6496

ACTION – Water-soluble antifungal agent with potent *in vivo* activity in rat models of systemic candidiasis (ED₅₀ = 5.3 µmol/kg i.v. and p.o.), pulmonary aspergillosis (ED₅₀ = 8.0 ± 4.2 µmol/kg i.v. and 7.4 ± 3.8 µmol/kg p.o.) and systemic aspergillosis (ED₅₀ = 3.0 µmol/kg i.v. and 5.8 µmol/kg p.o.), reported to be particularly suitable for parenteral administration. Compound is also reported to be chemically stable in aqueous solution at room temperature for more than 3 days but is readily converted to the corresponding triazole compound when incubated in mouse, rat, monkey or human plasma, thus acting as a prodrug. Another compound from this series of 3-[4-(4-cyanophenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ols and their corresponding *N*-benzyltriazolium derivatives is:



281150: C22 H17 F2 N5 O S

SOURCE – Roche.

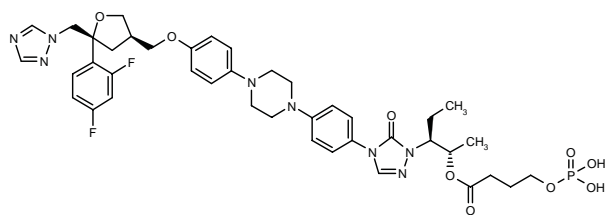
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SCH-59884

280850

4-(Phosphonoxy)butyric acid 2(*S*)-[4-[4-[4-[5(*R*)-(2,4-difluorophenyl)-5-(1*H*-1,2,4-triazol-1-ylmethyl)tetrahydrofuran-3(*R*)-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-1(*S*)-methylbutyl ester



C41 H49 F2 N8 O9 P; Mol wt: 866.8551

ACTION – A phosphate ester prodrug of the oral antifungal agent Sch-56592⁺ for i.v. administration; it was not active *in vitro* but showed potent antifungal activity *in vivo* against pulmonary *Aspergillus* and systemic *Candida* infections in mice (PD₅₀ = 7.1 and 0.8 mg/kg i.v., respectively). *In vivo*, it was rapidly dephosphorylated to the active metabolite Sch-207962 by liver, lung and kidney fractions; Sch-207962 was further hydrolyzed to Sch-56592 primarily by the liver fractions and serum. Potentially useful for the intravenous treatment of systemic and pulmonary fungal infections.

SOURCE – Schering-Plough.

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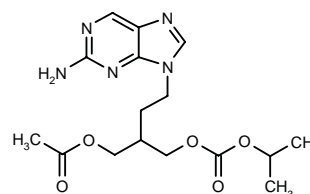
⁺Drug Data Rep 1995, 017(11): 1032.

ANTIVIRAL DRUGS

279899

Acetic acid 4-(2-amino-9*H*-purin-9-yl)-2-(isopropoxycarbonyloxymethyl)butyl ester

9-[4-(Acetoxy)-3-(isopropoxycarbonyloxymethyl)butyl]-2-aminopurine



C16 H23 N5 O5; Mol wt: 365.3877

ACTION – Antiviral agent, a prodrug of penciclovir affording high mean urinary recovery of penciclovir in mice (53%) and rats (36%) following oral administration. Compound showed good antiviral efficacy in HIV-1-infected mice, superior to the two penciclovir prodrugs famciclovir and valaciclovir in terms of survival rate (100, 80 and 40%, respectively) and mean survival time (> 21, 13 and 13 days, respectively), at doses of 0.075 mmol/kg p.o. b.i.d. for 5 days. Compound also showed good efficacy in duck hepatitis B virus (DHBV)-infected ducklings, without inducing signs of hepatotoxicity after 4 weeks of treatment.

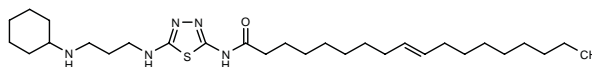
SOURCE – SK Chemicals.

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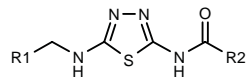
281323

N-[5-[3-(Cyclohexylamino)propylamino]-1,3,4-thiadiazol-2-yl]octadec-9(*E*)-enamide



C29 H53 N5 O S; Mol wt: 519.8377

ACTION – Antiviral agent particularly useful for the treatment or prevention of herpesvirus infections, and especially human cytomegalovirus (CMV) infections. It produced complete inhibition of CMV polymerase at a concentration of 25 μM. A representative compound from a series of 1,3,4-thiadiazoles, wherein the following are also included:



Compound	R1	R2	Formula
281324	CH2CH2NH-cyclohexyl	1,3-dioxo-1,3-dihydro-isobenzofuran-5-yl	C ₂₀ H ₂₃ N ₅ O ₄ S
281325	cyclohexyl	1,3-dioxo-1,3-dihydro-isobenzofuran-5-yl	C ₁₈ H ₁₈ N ₄ O ₄ S
281326	C10H21	1,3-dioxo-1,3-dihydro-isobenzofuran-5-yl	C ₂₂ H ₂₆ N ₄ O ₄ S
281327	1-Me-2-pyrrolidinyl-CH2	(CH2)7CH=CH-(CH2)7Me	C ₂₇ H ₄₀ N ₅ OS
281328	CH2NHPh	1,3-dioxo-1,3-dihydro-isobenzofuran-5-yl	C ₁₉ H ₁₅ N ₅ O ₄ S

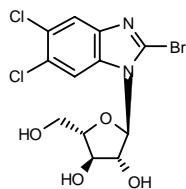
SOURCE – Pharmacia & Upjohn.

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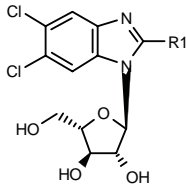
281909

2-Bromo-5,6-dichloro-1-(α-L-arabinofuranosyl)benzimidazole



C12 H11 Br Cl2 N2 O4; Mol wt: 398.0389

ACTION – Antiviral agent with an IC₅₀ value of 21 μM against human cytomegalovirus (HCMV) in infected HFF cells and low cytotoxicity in uninfected cells (> 100 μM). Other compounds from this series of arabinofuranosyl benzimidazoles include the following:



Compound	R1	Formula
281910	NHMe	C ₁₃ H ₁₅ Cl ₂ N ₃ O ₄
281911	Cl	C ₁₂ H ₁₁ Cl ₃ N ₂ O ₄
281912	i-PrNH	C ₁₅ H ₁₉ Cl ₂ N ₃ O ₄
281913	cyclopropyl-NH	C ₁₅ H ₁₇ Cl ₂ N ₃ O ₄
281914	cycloheptyl-NH	C ₁₉ H ₂₅ Cl ₂ N ₃ O ₄

SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

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LIPOSOMAL ODG-PFA-OMe^{3,4}

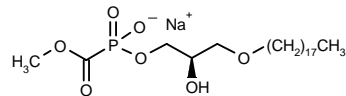
280591

Liposomal formulation of ODG-PFA-OMe in dioleoyl-phosphatidylcholine (PC) and cholesterol (CH) in a molar ratio PC:CH:drug of 65:20:15

ODG-PFA-OMe

280524

Hydroxy[2(*R*)-hydroxy-3-(octadecyloxy)propoxy]phosphorylcarboxylic acid methyl ester sodium salt



23 H47 Na O7 P; Mol wt: 488.5734

ACTION – Long-acting lipid prodrug of foscarnet with potent activity against human cytomegalovirus (HCMV; IC₅₀ = 1.08 and 40 μM for compound and foscarnet, respectively). After intravitreal injection, liposomal ODG-PFA-OMe showed good ocular vitreous compatibility in rabbits, with no retinal toxicity, no cataracts and no vitreous opacity at doses of up to 1.12, 0.632 and 0.84 mM, respectively. Potentially useful as an intravitreal treatment for CMV retinitis.

SOURCE – University of California, Oakland, Oakland, CA (US).

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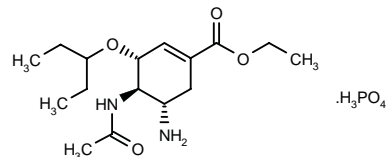
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OSELTAMIVIR PHOSPHATE*

241104

(3*R*,4*R*,5*S*)-4-Acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester phosphate (1:1)

GS-4104⁺ (free base)
GS-4104/002
Ro-64-0796 (free base)
Ro-64-0796/002



C16 H28 N2 O4 . H3 O4 P; Mol wt: 410.4009

ACTION – Oral antiviral agent, an ethyl ester prodrug that is hydrolyzed to the active form (oseltamivir carboxylate, GS-4071), which inhibits influenza virus neuraminidase.

INDICATION – Treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for not more than 2 days.

PRESENTATION – Capsules, equivalent to 75 mg free base.

PROPRIETARY NAME – *Tamiflu* (CH).

SOURCES – Gilead; licensed to Roche for codevelopment and marketing.

RECENT REFERENCES

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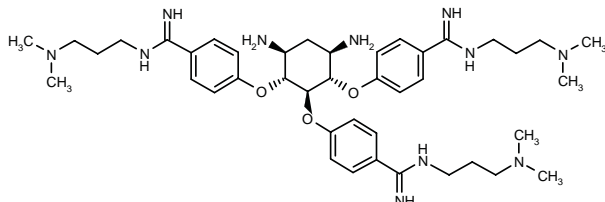
MONOGRAPH – Graul, A. et al. *Oseltamivir phosphate*. Drugs Fut 1999, 24(11): 1189.

+Drug Data Rep 1997, 019(05): 0444.

AIDS MEDICINES

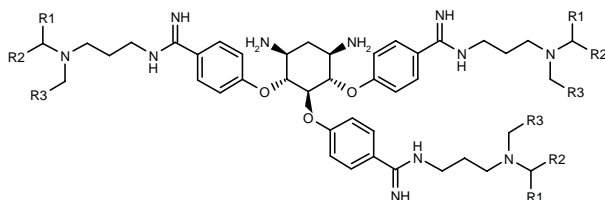
280361

[1*R*-(1 α ,2 β ,3 α ,4 β ,5 α)]-2,3,4-Tris[4-[*N*-[3-(dimethylamino)propyl]amidino]phenoxy]cyclohexane-1,5-diamine

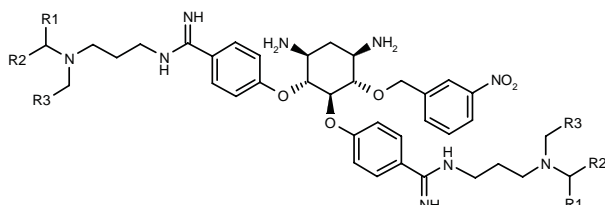


C42 H65 N11 O3; Mol wt: 772.0495

ACTION – Antiviral agent for AIDS that acts by inhibiting the binding of the HIV Rev protein to the virally encoded RNA sequence termed Rev-responsive element (RRE), considered to be critical for viral replication. Other compounds from this series of 2-deoxystreptamine derivatives include the following:



Compound	R1	R2	R3	Formula
280362	H	Me	Me	C ₄₈ H ₇₇ N ₁₁ O ₃
280363	Me	-(CH ₂) ₃ -		C ₅₄ H ₈₃ N ₁₁ O ₃



Compound	R1	R2	R3	Formula
280364	H	H	H	C ₃₇ H ₅₃ N ₉ O ₅
280365	H	Me	Me	C ₄₁ H ₆₁ N ₉ O ₅
280366	Me	-(CH ₂) ₃ -		C ₄₅ H ₆₅ N ₉ O ₅

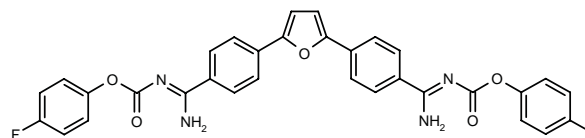
SOURCE – Scriptgen.

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280778

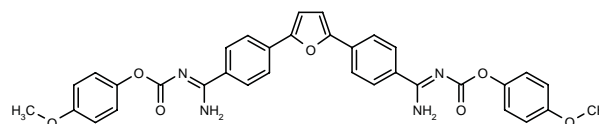
4,4'-(Furan-2,5-diyl)bis[*N*-(4-fluorophenoxy)carbonyl]-benzamide]



C32 H22 F2 N4 O5; Mol wt: 580.5448

Yellow solid, m.p. > 300 °C.

ACTION – Agent for the treatment of *Pneumocystis carinii* pneumonia proven to protect immunosuppressed mice from *P. carinii* infection at doses of 22 μ mol/kg i.v. and 33 μ mol/kg i.p., without toxicity. Potentially useful for the treatment of opportunistic infections in AIDS patients. Within this series of carbamate prodrugs, the following is also included:



280779: C34 H28 N4 O7

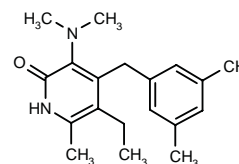
SOURCES – Georgia State University, Atlanta, GA (US); University of North Carolina, Chapel Hill, NC (US).

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282469

3-(Dimethylamino)-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1*H*)-one



C19 H26 N2 O; Mol wt: 298.4274

ACTION – A specifically claimed compound from a series of 3-(amino- or aminoalkyl)pyridinone derivatives that inhibits HIV reverse transcriptase (IC₅₀ = 20 nM) and demonstrates potent and selective anti-HIV-1 activity using a variety of strains and cell lines, giving IC₅₀ values of 0.004-2.4 nM versus CC₅₀ values of > 1000 nM.

SOURCES – CNRS; Institut Curie, Paris (FR).

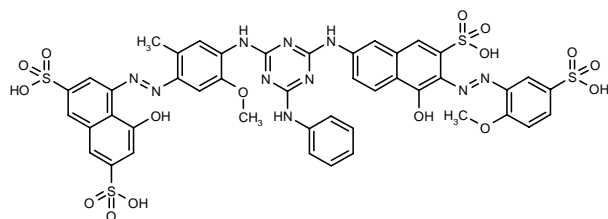
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ADS-J1

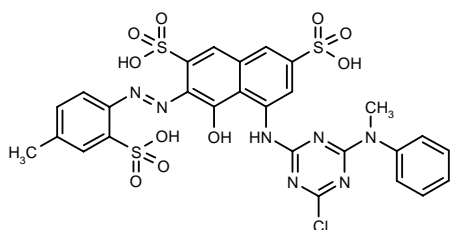
279107

4-[2-[4-[6-[5-Hydroxy-6-[2-(2-methoxy-5-sulfophenyl)-diazeryl]-7-sulfo-2-naphthylamino]-4-(phenylamino)-1,3,5-triazin-2-ylamino]-5-methoxy-2-methylphenyl]-diazeryl]-5-hydroxy-2,7-naphthalenedisulfonic acid



C44 H36 N10 O16 S4; Mol wt: 1089.0860

ACTION – Anti-HIV agent proven to inhibit HIV-1-mediated cell fusion and cytopathic effect (IC_{50} = 4.95 and 8.29 μ M, respectively); it inhibited the formation of MAB NC-1-detectable N-36/C-34 complex (IC_{50} = 0.73 μ M), suggesting that it inhibits HIV-1 infection by targeting the HIV-1 envelope glycoprotein gp41 core structure. The compound showed low cytotoxicity (CC_{50} = 292 μ M in uninfected MT-2 cells). Another related compound is:



ADS-J2 [279108]: C27 H22 Cl N7 O10 S3

SOURCE – New York Blood Center, New York, NY (US).

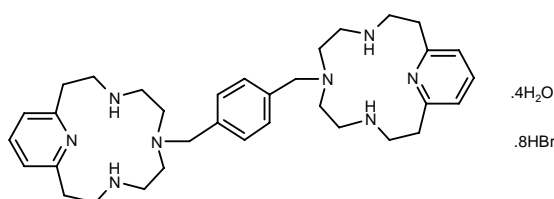
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AMD-3329*

226754

7,7'-(1,4-Phenylene)bis(methylene)bis[4,7,10,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene] octahydrobromide tetrahydrate



C34 H50 N8 . 8HBr . 4H2O; Mol wt: 1290.1900

ACTION – Anti-HIV agent proven to inhibit HIV-1 and HIV-2 replication in MT-4 cells (EC_{50} = 0.8 and 1.6 nM, respectively) with a high therapeutic index (CC_{50} = 194 μ M in uninfected MT-4 cells). Compound interfered with virus-

induced syncytium formation between chronically HIV-1-infected HUT-78 cells and uninfected MOLT-4 cells (EC_{50} = 12 nM), and it inhibited the binding of a specific anti-CXCR4 monoclonal antibody and Ca^{2+} flux induced by SDF-1 α in SUP-T1 cells.

SOURCES – AnorMED; Johnson Matthey.

REFERENCES

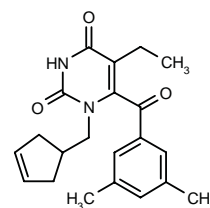
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*Identified compound **226754** Drug Data Rep 1995, 017(11): 1034.

SJ-3366*

256233

1-(3-Cyclopenten-1-ylmethyl)-6-(3,5-dimethylbenzoyl)-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione



C21 H24 N2 O3; Mol wt: 352.4370

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase inhibitor (NNRTI) able to inhibit the *in vitro* replication of both HIV-1 (IC_{50} = 0.1 nM), with a therapeutic index of approximately 4,000,000, and HIV-2 (IC_{50} = 150 nM), with a therapeutic index of almost 20,000. In addition to blocking HIV-1 RT, compound also inhibited virus attachment for both HIV-1 (IC_{50} = 10 nM) and HIV-2. It is equipotent against all strains of HIV-1 tested and interacts synergistically with didanosine and has additive effects with other anti-HIV agents tested, with no antagonism or synergistic toxicity. Like other NNRTIs, it has reduced activity against HIV-1 strains possessing Y181C, K103N or Y188C mutations.

SOURCE – Samjin.

REFERENCES

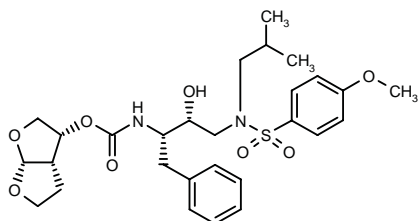
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2. Buckheit, R.W. et al. *Therapeutic potential of a new nonnucleoside reverse transcriptase inhibitor of HIV-1 with activity against HIV-2*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F926.
3. Buckheit, R.W. Jr. et al. *Combination anti-HIV and resistance profile for SJ-3366: A new non-nucleoside reverse transcriptase inhibitor of HIV-1 with activity against HIV-2*. Antivir Ther 1999, 4(Suppl. 1): Abst 4.
4. Lackman-Smith, C. et al. *A highly potent NNRTI possessing potential dual activity against HIV-1 reverse transcriptase and chemokine receptor interactions*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F925.

*Identified compound **256233** (see **255070**) Drug Data Rep 1997, 019(11): 1024.

UIC-94-003

280792

N-[1(*S*)-Benzyl-2(*R*)-hydroxy-3-[*N*-isobutyl-*N*-(4-methoxyphenylsulfonyl)amino]propyl]carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester



C₂₈ H₃₈ N₂ O₈ S; Mol wt: 562.6802

ACTION – Anti-HIV agent, an inhibitor of HIV-1 protease ($K_i = 1.1$ nM) with antiviral activity in both acutely and chronically infected cells. In acutely infected H9 cells, compound concentration-dependently (1-50 nM) inhibited virus production, and in chronically infected H9/HIV-1_{IIIB} cells, continuous exposure to compound (5-50 nM) resulted in 90% inhibition of virus production on days 7-11, being approximately 5-fold more potent than saquinavir.

SOURCES – Finch University of Health Sciences/The Chicago Medical School, Chicago, IL (US); University of Illinois, Chicago (US); University of the Pacific, Stockton, CA (US).

REFERENCES

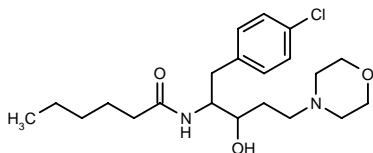
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2. Ghosh, A.K. et al. *Potent HIV protease inhibitors incorporating high-affinity P2-ligands and (R)-(hydroxyethylamino)sulfonamide isostere*. Bioorg Med Chem Lett 1998, 8(6): 687.

TREATMENT OF PROTOZOAL DISEASES

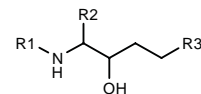
282460

N-[1-(4-Chlorobenzyl)-2-hydroxy-4-(4-morpholinyl)-butyl]hexanamide



C₂₁ H₃₃ Cl N₂ O₃; Mol wt: 396.9557

ACTION – An inhibitor of aspartyl proteases with selective inhibitory activity against plasmepsin and cathepsin D and potential in the treatment of malaria, Alzheimer's disease, connective tissue disease, muscular dystrophy and breast cancer. Other exemplified compounds from this series of hydroxypropylamide derivatives are:



Compound	R1	R2	R3	Formula
282461	COPh	CH ₂ Ph	OCONHPh	C ₂₅ H ₂₈ N ₂ O ₄
282462	COPh	i-Bu	N(Ac)CH ₂ Ph	C ₂₄ H ₃₂ N ₂ O ₃
282463	3,4-(Cl)2-PhCO	3,4-(Cl)2-PhCH ₂	1-indanyl-N(SO ₂ Me)	C ₂₈ H ₂₈ Cl ₄ N ₂ O ₄ S
282464	PhCO-L-Leu-	(S)-i-Bu	N(Ac)CH ₂ Ph	C ₃₀ H ₄₃ N ₃ O ₄

SOURCE – Pharmacopeia.

REFERENCES

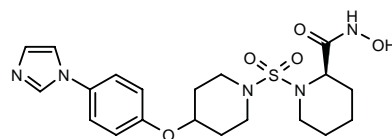
1. Dolle, R.E. III and Cavallaro, C.L. (Pharmacopeia, Inc.) *Hydroxypropylamide peptidomimetics as inhibitors of aspartyl proteases*. WO 9955687.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

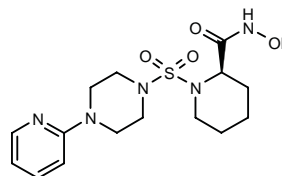
279798²

1-[4-[4-(1*H*-Imidazol-1-yl)phenoxy]piperidin-1-ylsulfonyl]-piperidine-2(*R*)-carboxyhydroxamic acid



C₂₀ H₂₇ N₅ O₅ S; Mol wt: 449.5293

ACTION – Matrix metalloproteinase (MMP) inhibitor with high selectivity for gelatinase A and collagenase 3 (IC₅₀ = 0.033 and 0.068 nM, respectively) over collagenase 1 (fibroblast collagenase) and matrilysin (IC₅₀ = 224 and 304 nM, respectively); it also potently inhibits human stromelysin (IC₅₀ = 0.258 nM). Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis, tumor metastasis and periodontal disease. Within this series of pipercolinic sulfamides and sulfonamides, the following is also included:



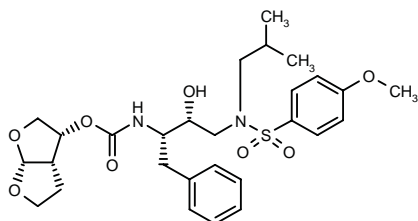
279797:^{1,2} C₁₅ H₂₃ N₅ O₄ S

SOURCES – Agouron (Warner-Lambert); Roche Bioscience.

UIC-94-003

280792

N-[1(*S*)-Benzyl-2(*R*)-hydroxy-3-[*N*-isobutyl-*N*-(4-methoxyphenylsulfonyl)amino]propyl]carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester



C₂₈ H₃₈ N₂ O₈ S; Mol wt: 562.6802

ACTION – Anti-HIV agent, an inhibitor of HIV-1 protease ($K_i = 1.1$ nM) with antiviral activity in both acutely and chronically infected cells. In acutely infected H9 cells, compound concentration-dependently (1-50 nM) inhibited virus production, and in chronically infected H9/HIV-1_{IIIB} cells, continuous exposure to compound (5-50 nM) resulted in 90% inhibition of virus production on days 7-11, being approximately 5-fold more potent than saquinavir.

SOURCES – Finch University of Health Sciences/The Chicago Medical School, Chicago, IL (US); University of Illinois, Chicago (US); University of the Pacific, Stockton, CA (US).

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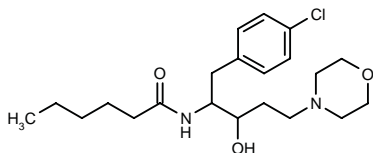
1. Ghosh, A.K. et al. *Antiviral activity of UIC-94-003, a novel inhibitor of the human immunodeficiency virus type 1 protease*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F928.

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TREATMENT OF PROTOZOAL DISEASES

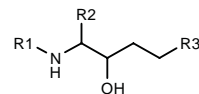
282460

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282463	3,4-(Cl)2-PhCO	3,4-(Cl)2-PhCH ₂	1-indanyl-N(SO ₂ Me)	C ₂₈ H ₂₈ Cl ₄ N ₂ O ₄ S
282464	PhCO-L-Leu-	(S)-i-Bu	N(Ac)CH ₂ Ph	C ₃₀ H ₄₃ N ₃ O ₄

SOURCE – Pharmacopeia.

REFERENCES

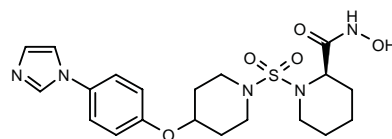
1. Dolle, R.E. III and Cavallaro, C.L. (Pharmacopeia, Inc.) *Hydroxypropylamide peptidomimetics as inhibitors of aspartyl proteases*. WO 9955687.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

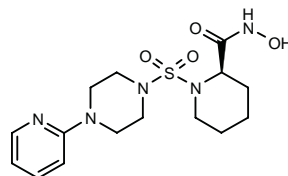
279798²

1-[4-[4-(1*H*-Imidazol-1-yl)phenoxy]piperidin-1-ylsulfonyl]-piperidine-2(*R*)-carboxyhydroxamic acid



C₂₀ H₂₇ N₅ O₅ S; Mol wt: 449.5293

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279797:^{1,2} C₁₅ H₂₃ N₅ O₄ S

SOURCES – Agouron (Warner-Lambert); Roche Bioscience.

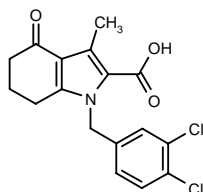
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2. Mitchell, L.J. Jr. et al. *Novel sulfamides and sulfonamide inhibitors of matrix metalloproteases*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MED1 76.

280017

1-(3,4-Dichlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid



C17 H15 Cl2 N O3; Mol wt: 352.2155

ACTION – Monocyte chemoattractant protein-1 (MCP-1) receptor antagonist (IC_{50} = 0.4 μ M against [125 I]-MCP-1 binding to the human MCP-1 receptor B cloned in CHO cells) with potential in the treatment of rheumatoid arthritis, glomerulonephritis, lung fibrosis, restenosis, asthma, atherosclerosis, psoriasis, delayed-type hypersensitivity skin reactions, inflammatory bowel disease, multiple sclerosis, brain trauma, stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection. A representative compound from a series of bicyclic pyrrole derivatives.

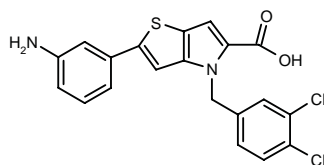
SOURCE – AstraZeneca.

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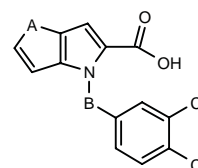
280018

2-(3-Aminophenyl)-4-(3,4-dichlorobenzyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid



C20 H14 Cl2 N2 O2 S; Mol wt: 417.3146

ACTION – Monocyte chemoattractant protein-1 (MCP-1) receptor antagonist (IC_{50} = 8.3 μ M against [125 I]-MCP-1 binding to the human MCP-1 receptor B cloned in CHO cells) with potential in the treatment of rheumatoid arthritis, glomerulonephritis, lung fibrosis, restenosis, asthma, atherosclerosis, psoriasis, delayed-type hypersensitivity skin reactions, inflammatory bowel disease, multiple sclerosis, brain trauma, stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection. Within this series of bicyclic pyrrole derivatives, the following are also included:



Compound	A	B	Formula
280019	S	CH2	C ₁₄ H ₉ Cl ₂ NO ₂ S
280020	O	SO2	C ₁₃ H ₇ Cl ₂ NO ₅ S

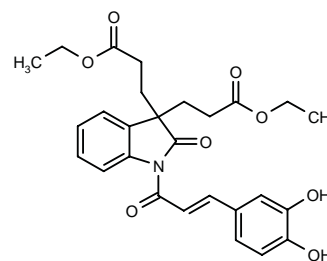
SOURCE – AstraZeneca.

REFERENCES

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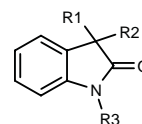
280404

1-[3-(3,4-Dihydroxyphenyl)-2(E)-propenoyl]-2-oxo-2,3-dihydro-1H-indole-3,3-dipropionic acid diethyl ester



C27 H29 N O8; Mol wt: 495.5251

ACTION – Cytokine production inhibitor shown to inhibit the production of IL-1, IL-6 and TNF- α in lipopolysaccharide-stimulated human monocytes with IC_{50} values of 1.2, 4.2 and 3-6 μ M, respectively, as compared to IC_{50} values of > 50 μ M against all three cytokines for the reference compound tenidap. Other compounds from this series of 2-oxoindole derivatives include the following:



Compound	R1	R2	R3	Formula
280405	CH2CO2Et	H	3,4-(MeO)2-Ph-CH=CHCO	C ₂₃ H ₂₃ NO ₆
280406	CH2CH2CO2Et	CH2CH2CO2Et	3,4-(MeO)2-Ph-CH=CHCO	C ₂₉ H ₃₃ NO ₆
280407	-CH(CO2Et)-		Ph	C ₁₈ H ₁₅ NO ₃

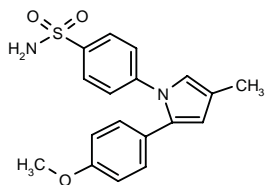
SOURCE – Maruho.

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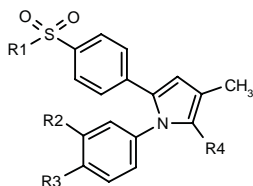
280412

4-[4-Methyl-2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl]benzenesulfonamide

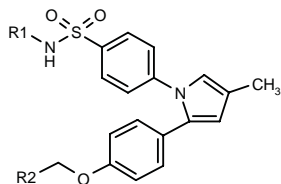


C18 H18 N2 O3 S; Mol wt: 342.4172

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; IC_{50} = 0.016 μ M for inhibition of PGE_2 production in COS cells expressing human COX-2) with > 6250-fold selectivity versus COX-1 (IC_{50} > 100 μ M). *In vivo*, compound exhibited analgesic activity in the yeast-induced hyperalgesia assay in rats at 12.5 mg/kg p.o., as well as against hot water-induced pain in rats (ID_{50} = 1.1 mg/kg p.o.), antipyretic activity in the yeast-induced fever assay in rats (82% inhibition at 0.4 mg/kg p.o.) and antiinflammatory activity in the carrageenan-induced paw edema model in rats (65% inhibition at 50 mg/kg p.o.). It had low ulcerogenic potential in rats (UD_{50} > 100 mg/kg p.o.). Within this series of 1,2-diphenylpyrrole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
280413	Me	H	F	Br	C ₁₈ H ₁₅ BrFNO ₂ S
280414	Me	Me	Me	H	C ₂₀ H ₂₁ NO ₂ S
280417	NH ₂	-OCH ₂ O-	H		C ₁₈ H ₁₆ N ₂ O ₄ S



Compound	R1	R2	Formula
280415	H	Me	C ₁₉ H ₂₀ N ₂ O ₃ S
280416	Ac	H	C ₂₀ H ₂₀ N ₂ O ₄ S

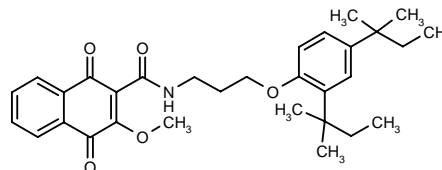
SOURCE – Sankyo.

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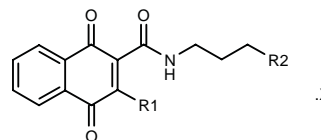
280562

N-[3-[2,4-Bis(1,1-dimethylpropyl)phenoxy]propyl]-3-methoxy-1,4-dioxo-1,4-dihydronaphthalene-2-carboxamide



C31 H39 N O5; Mol wt: 505.6511

ACTION – Immunosuppressant found to potently inhibit PHA-stimulated human T-cell proliferation (IC_{50} < 0.10 μ g/ml), as well as the murine mixed lymphocyte reaction (IC_{50} = 0.37 μ g/ml); it was active against collagen-induced arthritis in mice at 50 mg/kg/day i.p. x 2 weeks. Other compounds from this series of naphthoquinone derivatives include the following:



Compound	R1	R2	X	Formula
280565	OH	OC ₁₂ H ₂₅		C ₂₆ H ₃₇ NO ₅
280566	OH	4-[t-BuCH ₂ C(Me) ₂]-PhO		C ₂₈ H ₃₃ NO ₅
280567	OH	2,4-[EtC(Me) ₂]-PhO		C ₃₀ H ₃₇ NO ₅
280568	OH	2,4-[EtC(Me) ₂]-PhO	NH(Me) ₂	C ₃₀ H ₃₇ NO ₅ ·C ₂ H ₇ N
280570	OMe	C ₉ H ₁₉		C ₂₄ H ₃₃ NO ₄
280571	N(Me) ₂	2,4-[EtC(Me) ₂]-PhO		C ₃₂ H ₄₂ N ₂ O ₄

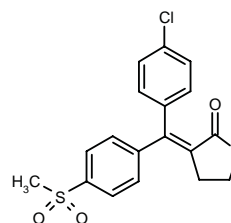
SOURCE – Fuji Photo Film.

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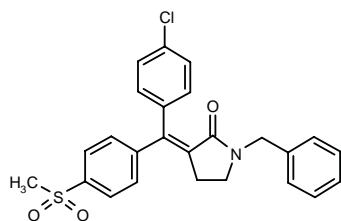
280589

3-[(*Z*)-1-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylene]tetrahydrothiophen-2-one



C18 H15 Cl O3 S2; Mol wt: 378.8985

ACTION – Antiinflammatory and analgesic agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor (IC_{50} = 0.12 μ M against purified enzyme from sheep placenta). Analgesic activity was shown in the kaolin-induced arthritis model in rats (ED_{50} = 13.7 mg/kg p.o.). Within this series of heterocyclic diarylmethylene derivatives, the following compound is also included:



280590: C₂₅ H₂₂ Cl N O₃ S

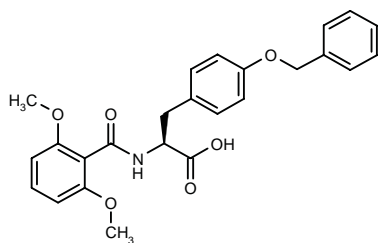
SOURCE – UPSA.

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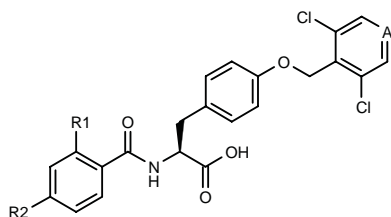
280594

O-Benzyl-N-(2,6-dimethoxybenzoyl)-L-tyrosine

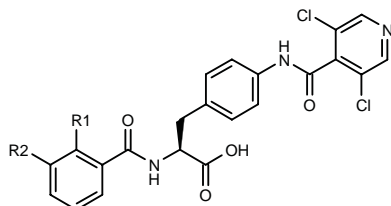


C₂₅ H₂₅ N O₆; Mol wt: 435.4735

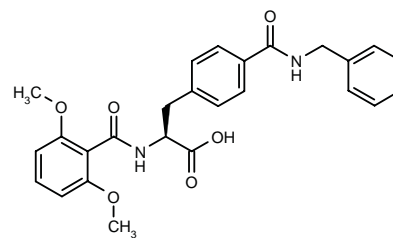
ACTION – Agent for the treatment of immune or inflammatory disorders that acts by selectively inhibiting the binding of α 4 integrins, particularly α 4 β 1 and α 4 β 7 integrins, to their ligands. Other specifically claimed phenylalanine derivatives include the following:



Compound	R1	R2	A	Formula
280597	4-Me-PhS	H	CH	C ₃₀ H ₂₅ Cl ₂ NO ₄ S
280601	H	Ph	N	C ₂₈ H ₂₂ Cl ₂ N ₂ O ₄



Compound	R1	R2	Formula
280599	CO ₂ H	H	C ₂₃ H ₁₇ Cl ₂ N ₃ O ₆
280602	H	CN	C ₂₃ H ₁₆ Cl ₂ N ₄ O ₄
280604	H	5-tetrazolyl	C ₂₃ H ₁₇ Cl ₂ N ₇ O ₄
280606	CO ₂ Me	H	C ₂₄ H ₁₉ Cl ₂ N ₃ O ₆



280600: C₂₆ H₂₆ N₂ O₆

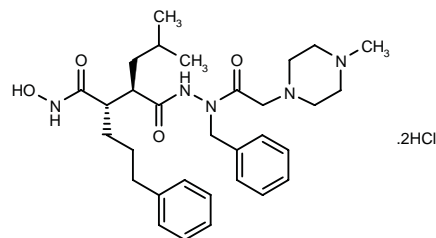
SOURCE – Celltech Chiroscience.

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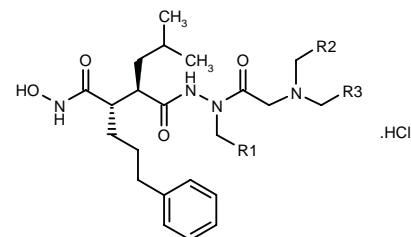
280638

5-Methyl-3-(R)-[3-benzyl-3-[2-(4-methylpiperazin-1-yl)-acetyl]carbazoyl]-2-(S)-(3-phenylpropyl)hexanohydroxamic acid dihydrochloride



C₃₁ H₄₅ N₅ O₄ . 2HCl; Mol wt: 624.6493

ACTION – An inhibitor of the production of TNF- α (IC₅₀ = 0.53 μ M in lipopolysaccharide-stimulated THP-1 cells) with good water solubility, potentially useful in the treatment or prevention of autoimmune and inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, Crohn's disease, cachexia, systemic lupus erythematosus, sepsis, asthma, type I diabetes and psoriasis. Other compounds from this series of azapeptide-type hydroxamic acids include the following:



Compound	R1	R2	R3	Formula
280639	Ph	-CH ₂ OCH ₂ -		C ₃₀ H ₄₂ N ₄ O ₅ .HCl
280640	Ph	H	H	C ₂₈ H ₄₀ N ₄ O ₄ .HCl
280641	CH ₂ Ph	-CH ₂ OCH ₂ -		C ₃₁ H ₄₄ N ₄ O ₅ .HCl

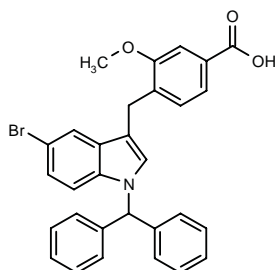
SOURCE – Yoshitomi.

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1. Sugiyama, N. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Novel azapeptide type hydroxamic acid derivs*. WO 9940063.

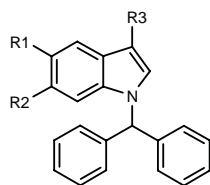
280666

4-[5-Bromo-1-(diphenylmethyl)-1*H*-indol-3-ylmethyl]-3-methoxybenzoic acid

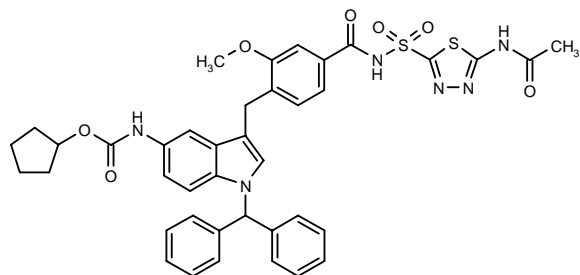


C30 H24 Br N O3; Mol wt: 526.4276

ACTION – Agent for the treatment of inflammatory disorders that acts via inhibition of phospholipase enzymes, particularly cytosolic phospholipase A₂ (cPLA₂; IC₅₀ = 0.39-0.95 μM in the coumarin assay). It proved active *in vivo* in the rat carrageenan-induced paw edema test (26% inhibition at 2 mg/kg p.o.). Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
280668	Br	H	2-MeO-4-(2-Me-Ph-SO ₂ NHCO)-PhCH ₂	C ₃₇ H ₃₁ BrN ₂ O ₄ S
280669	NO ₂	H	CH=CHCO ₂ H	C ₂₄ H ₁₈ N ₂ O ₄
280670	NO ₂	H	CH=CHCO-NHSO ₂ Me	C ₂₅ H ₂₁ N ₃ O ₅ S
280672	NHSO ₂ N(Me) ₂	H	2-MeO-4-CO ₂ H-PhCH ₂	C ₃₂ H ₃₁ N ₃ O ₅ S
280674	2-Me-PhSO ₂ NH	H	2-MeO-4-CO ₂ H-PhCH ₂	C ₃₇ H ₃₂ N ₂ O ₅ S
280675	3,5-(Me) ₂ -4-isoxazolyl-SO ₂ NH	H	2-MeO-4-CO ₂ H-PhCH ₂	C ₃₅ H ₃₁ N ₃ O ₆ S
280676	cyclopentyl-CONH	H	4-CO ₂ H-3-thienyl-NHCO	C ₃₃ H ₂₉ N ₃ O ₄ S
280677	-OCH ₂ O-		2-MeO-4-CO ₂ H-PhCH ₂	C ₃₁ H ₂₅ NO ₅



280678: C40 H38 N6 O7 S2

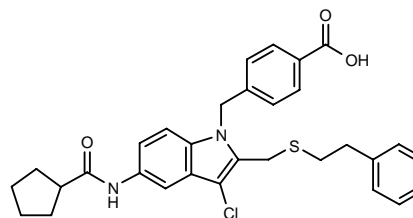
SOURCE – Genetics Institute.

REFERENCES

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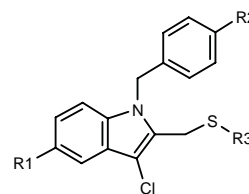
280695

4-[3-Chloro-5-(cyclopentylcarboxamido)-2-(2-phenylethylsulfanylmethyl)-1*H*-indol-1-ylmethyl]benzoic acid

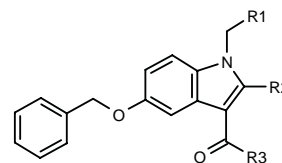


C31 H31 Cl N2 O3 S; Mol wt: 547.1159

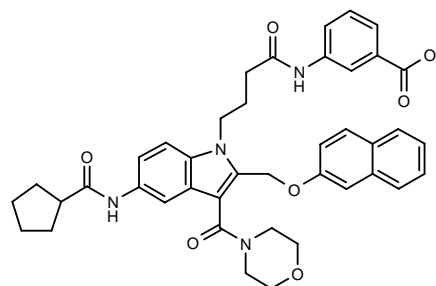
ACTION – Agent for the treatment of inflammatory disorders such as rheumatoid arthritis, psoriasis, asthma and inflammatory bowel disease, osteoporosis, myelogenous leukemia, diabetes and atherosclerosis that acts via inhibition of phospholipase enzymes, particularly cytosolic phospholipase A₂ (cPLA₂). Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
280696	cyclopentyl-CONH	CO ₂ H	cyclopropyl-CH ₂	C ₂₇ H ₂₉ ClN ₂ O ₃ S
280697	NHCONH-CH ₂ Ph	CO ₂ H	2-Naph	C ₃₅ H ₂₈ ClN ₃ O ₃ S
280699	t-BuCONH	CO ₂ H	2-Naph	C ₃₂ H ₂₉ ClN ₂ O ₃ S
280700	cyclopentyl-CON(Me)	CO ₂ H	2-Naph	C ₃₄ H ₃₁ ClN ₂ O ₃ S
280701	cyclopentyl-CONH	4-NO ₂ -Ph-SO ₂ NHCO	2-Naph	C ₃₉ H ₃₃ ClN ₄ O ₆ S ₂



Compound	R1	R2	R3	Formula
280702	4-(CH ₂ CO ₂ H)-Ph	H	2-Naph	C ₃₅ H ₂₇ NO ₄
280704	4-(CO ₂ H)-Ph-NHCOCH ₂ CH ₂	2-Naph-OCH ₂	Ph	C ₄₄ H ₃₆ N ₂ O ₆
280705	CH=CHCO ₂ H	2-Naph-OCH ₂	Ph	C ₃₇ H ₂₉ NO ₅



280706: C41 H42 N4 O7

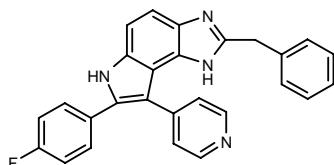
SOURCE – Genetics Institute.

REFERENCES

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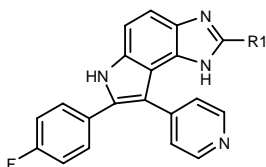
280815

2-Benzyl-7-(4-fluorophenyl)-8-(4-pyridinyl)-1,6-dihydro-pyrrolo[3,2-*e*]benzimidazole



C27 H19 F N4; Mol wt: 418.4731

ACTION – Antiinflammatory agent, an inhibitor of the production of cytokines, particularly TNF- α (IC_{50} = 7.0 nM) and IL-1 β , that is believed to act via inhibition of p38 kinase (44% inhibition at 20 μ M). *In vivo*, it was shown to inhibit lipopolysaccharide-induced TNF- α production in mice by 74 and 91% at 10 and 25 mg/kg p.o., respectively. Other specifically claimed compounds from this series of substituted pyrrolobenzimidazoles include the following:



Compound	R1	Formula
280818	Ph	C ₂₆ H ₁₇ FN ₄
280820	Bu	C ₂₄ H ₂₁ FN ₄
280821	CH ₂ CH ₂ Ph	C ₂₈ H ₂₁ FN ₄
280822	H	C ₂₀ H ₁₃ FN ₄

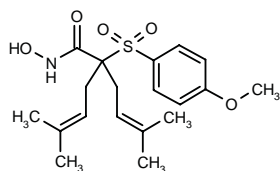
SOURCE – Ortho-McNeil.

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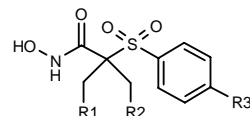
280857

2-(4-Methoxyphenylsulfonyl)-5-methyl-2-(3-methyl-2-butenyl)hex-4-enohydroxamic acid



C19 H27 N O5 S; Mol wt: 381.4903

ACTION – Matrix metalloproteinase (MMP) inhibitor found to be a particularly potent inhibitor of MMP-9 (gelatinase B; IC_{50} = 0.54 nM) and MMP-13 (collagenase 3; IC_{50} = 0.4 nM), and also of MMP-1 (fibroblast collagenase; IC_{50} = 25 nM), also shown to inhibit TNF- α -converting enzyme (TACE; IC_{50} = 805 nM). Potentially useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disorders, diabetes and HIV infection. Other exemplified compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	R3	Formula
280859	4-[N(Et)2CH2CH2O]-Ph	H	2-furyl	C ₂₆ H ₃₂ N ₂ O ₆ S
280860	2-Naph	H	OMe	C ₂₇ H ₂₁ NO ₅ S
280861	CH=C(Me)2	3-Pyr	OMe	C ₂₀ H ₂₄ N ₂ O ₅ S
280862	CH=C(Me)CH2-CH2CH=C(Me)2	H	OMe	C ₂₀ H ₂₉ NO ₅ S
280863	3-[N(Et)2CH2CH2O]-Ph	H	OMe	C ₂₃ H ₃₂ N ₂ O ₆ S
280864	-CH2N[4-(1-Pip-CH2CH2O)-PhCH2]CH2-		OMe	C ₂₇ H ₃₇ N ₃ O ₆ S
280865	-CH2N[4-(2-Pyr)-PhCH2]CH2-		OMe	C ₂₅ H ₂₇ N ₃ O ₅ S

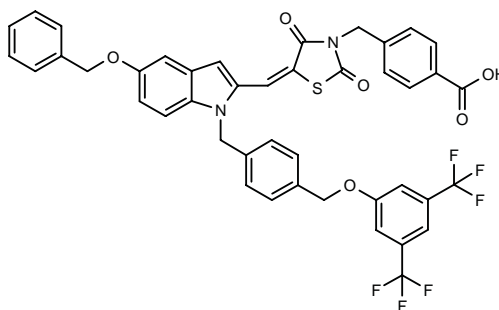
SOURCE – American Home Products.

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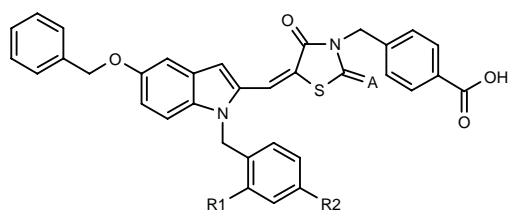
280894

4-[5(*E*)-[5-Benzoyloxy-1-[4-[3,5-bis(trifluoromethyl)-phenoxy]methyl]benzyl]-1*H*-indol-2-ylmethylene]-2,4-dioxothiazolidin-3-ylmethyl]benzoic acid

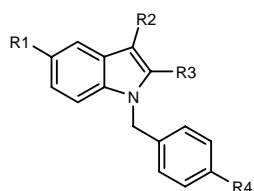


C43 H30 F6 N2 O6 S; Mol wt: 816.7720

ACTION – Agent for the treatment of inflammatory disorders that acts via inhibition of phospholipase enzymes, particularly cytosolic phospholipase A₂ (cPLA₂; IC_{50} = 3 μ M). Other related compounds include the following:



Compound	R1	R2	A	Formula
280895	H	Cl	O	C ₃₄ H ₂₅ ClN ₂ O ₃ S
280896	CF ₃	CF ₃	S	C ₃₆ H ₂₄ F ₆ N ₂ O ₄ S ₂



Compound	R1	R2	R3	R4	Formula
280897	OCH ₂ Ph	H	CO ₂ H	3,5-(CF ₃) ₂ -PhOCH ₂	C ₃₂ H ₂₃ F ₆ NO ₄
280898	H	H	3-CO ₂ H-PhNHCO	3,5-(CF ₃) ₂ -PhOCH ₂	C ₃₂ H ₂₂ F ₆ N ₂ O ₄
280899	OCH ₂ Ph	Ac	2-CO ₂ H-PhSCH ₂	2-benzothiazolyl-CO	C ₄₀ H ₃₀ N ₂ O ₅ S ₂

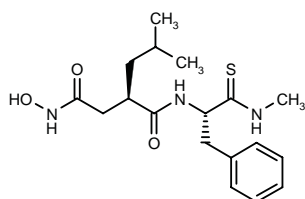
SOURCE – Genetics Institute.

REFERENCES

1. Seehra, J.S. et al. (Genetics Institute Inc.) *Inhibitors of phospholipase A₂*. WO 9943672.

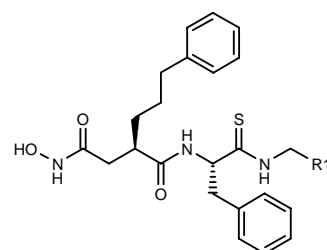
280949

*N*⁴-Hydroxy-2(*R*)-isobutyl-*N*¹-[1(*S*)-(N-methylthiocarbamoyl)-2-phenylethyl]succinamide



C18 H27 N3 O3 S; Mol wt: 365.4953

ACTION – Matrix metalloproteinase (MMP) and TNF- α production inhibitor with IC₅₀ values of 1 nM against MMP-2/3 (gelatinase A/stromelysin) and MMP-9 (gelatinase B), reported to possess good oral bioavailability and an improved duration of action and pharmacokinetic profile as compared to structurally related compounds. Potentially useful for the treatment of disorders involving tissue breakdown and inflammation such as osteoarthritis, rheumatoid arthritis, osteoporosis and tumor metastasis, among others. Other exemplified compounds include the following:



Compound	R1	Formula
280950	H	C ₂₃ H ₂₉ N ₃ O ₃ S
280951	CH ₂ CH ₂ Ph	C ₃₁ H ₃₇ N ₃ O ₃ S

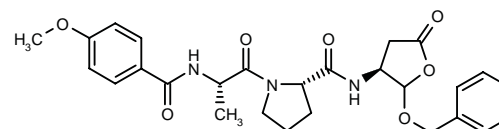
SOURCE – Leo.

REFERENCES

1. Christensen, M.K. (Leo Pharmaceutical Products Ltd. A/S) *Matrix metalloproteinase inhibitors*. WO 9944989.

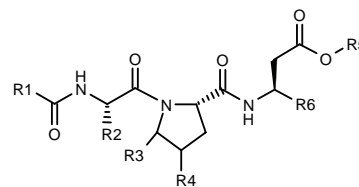
281295

1-[*N*-(4-Methoxybenzoyl)-L-alanyl]-*N*-[2-(benzyloxy)-5-oxotetrahydrofuran-3(*S*)-yl]-L-prolinamide



C27 H31 N3 O7; Mol wt: 509.5559

ACTION – An inhibitor of caspases, in particular IL-1 β -converting enzyme (ICE or caspase 1), with good oral bioavailability (> 67% in rats). Potentially useful for the treatment of IL-1-, apoptosis-, interferon gamma- or interferon gamma-inducing factor (IGIF)-mediated diseases such as inflammatory, autoimmune, proliferative, destructive bone, infectious and degenerative diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
281296	4-MeO-3,5-(Me) ₂ -Ph	Me	H	H	-CH(OCH ₂ Ph)-		C ₂₉ H ₃₅ N ₃ O ₇
281297	4-NH ₂ -3-Cl-Ph	Me	H	H	-CH(OCH ₂ Ph)-		C ₂₆ H ₂₉ ClN ₄ O ₆
281298	4-(AcNH)-Ph	i-Pr	H	H	H	CHO	C ₂₃ H ₃₀ N ₄ O ₇
281299	1-isoquinolyl	Me	-(CH ₂) ₄ -	H	CHO		C ₂₆ H ₃₀ N ₄ O ₆

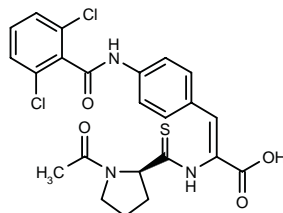
SOURCE – Vertex.

REFERENCES

1. Wannamaker, M.W. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of caspases*. WO 9947545.

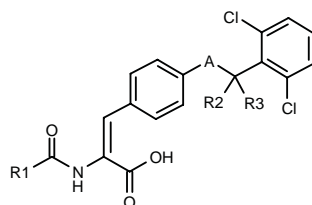
281320

2-[1-Acetylpyrrolidin-2(*R*)-ylthiocarboxamido]-3-[4-(2,6-dichlorobenzamido)phenyl]-2(*Z*)-propenoic acid



C23 H21 Cl2 N3 O4 S; Mol wt: 506.4079

ACTION – Agent for the treatment of immune or inflammatory disorders, a potent and selective inhibitor of $\alpha 4$ integrins such as $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins. Other specifically claimed compounds from this series of cinnamic acid derivatives include the following:



Compound	R1	R2	R3	A	Isomer	Formula
281321	2-Cl-3-Pyr	H	H	O	Z	C ₂₂ H ₁₅ Cl ₃ N ₂ O ₄
281322	t-Bu	-O-	NH	E	E	C ₂₁ H ₂₀ Cl ₂ N ₂ O ₄

SOURCE – Celltech Chiroscience.

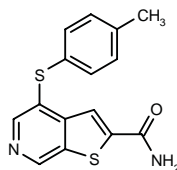
REFERENCES

1. Archibald, S.C. et al. (Celltech Chiroscience plc) *Cinnamic acid derivs. having cell adhesion modulating activity*. WO 9947547.

A-205804

279527

4-(4-Methylphenylsulfanyl)thieno[2,3-*c*]pyridine-2-carboxamide



C15 H12 N2 O S2; Mol wt: 300.4048

ACTION – Potent inhibitor of the expression of the adhesion molecules E-selectin and ICAM-1 in human endothelial cells (IC_{50} = 0.02 and 0.025 μ M, respectively, in a CAM assay), with good selectivity over VCAM-1 (IC_{50} > 1 μ M). Compound was noncytotoxic to human umbilical vein endothelial cells (HUVEC; IC_{50} = 152 μ M) and was selected as a lead compound for further studies.

SOURCES – Abbott; ICOS.

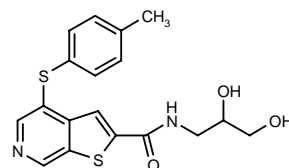
REFERENCES

1. Stewart, A.O. et al. (Abbott Laboratories, Inc.) *Cell adhesion-inhibiting antiinflammatory cpds*. WO 9962908.
2. Boyd, S.A. et al. *Discovery of inhibitors of cell adhesion molecule expression in human endothelial cells: Selective inhibition of ICAM-1 and E-selectin expression*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 73.

A-241548

279800

N-(2,3-Dihydroxypropyl)-4-(4-methylphenylsulfanyl)-thieno[2,3-*c*]pyridine-2-carboxamide



C18 H18 N2 O3 S2; Mol wt: 374.4832

ACTION – An inhibitor of adhesion molecule expression with good selectivity for E-selectin and ICAM-1 (IC_{50} = 0.62 and 0.60 μ M, respectively) over VCAM-1 (41% inhibition at 4 μ M) and low toxicity against human umbilical vein endothelial cells (HUVEC; IC_{50} = 74 μ M). It showed significantly improved pharmacokinetics compared to the parent compound A-205804.0 (A-205804).

SOURCES – Abbott; ICOS.

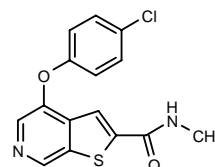
REFERENCES

1. Stewart, A.O. et al. (Abbott Laboratories, Inc.) *Cell adhesion-inhibiting antiinflammatory cpds*. WO 9962908.
2. Staeger, M.A. et al. *Discovery of inhibitors of cell adhesion molecule expression in human endothelial cells: Selective inhibition of ICAM-1 and E-selectin expression*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 74.

A-252444.0

279801

4-(4-Chlorophenoxy)-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide



C15 H11 Cl N2 O2 S; Mol wt: 318.7829

ACTION – Potent inhibitor of E-selectin and ICAM-1 expression in human endothelial cells (IC_{50} = 0.012 and 0.02 μ M, respectively) with 20-40-fold selectivity over VCAM-1 (IC_{50} = 0.49 μ M). Compound showed improved water solubility (1.2 μ g/ml vs. 0.3 μ g/ml) and oral bioavailability when compared with the parent compound A-205804.0 (A-205804), as well as good metabolic stability.

SOURCES – Abbott; ICOS.

REFERENCES

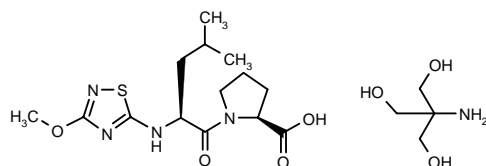
1. Stewart, A.O. et al. (Abbott Laboratories, Inc.) *Cell adhesion-inhibiting antiinflammatory cpds*. WO 9962908.

2. Arendsen, D.L. et al. *Inhibitors of cell adhesion molecule expression in human endothelial cells: Modification of 2-position of 4-aryloxythieno [2,3-c]pyridines*. 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 75.

APO-501

280948

N-(3-Methoxy-1,2,4-thiadiazol-5-yl)-L-leucyl-L-proline tromethamine salt



C14 H22 N4 O4 S . C4 H11 N O3; Mol wt: 463.5527

ACTION – A representative compound from a series of thiadiazole derivatives that inhibits cysteine activity-dependent enzymes, particularly human transglutaminase, rhinovirus 3C protease and cathepsin B. It inhibited IL-1-induced proteoglycan degradation of calf joint articular cartilage by 60% at a concentration of 1 μ M, and the free acid inhibited cathepsin B by 85% at 60 mM. It is expected to be useful in the treatment of inflammatory joint diseases, the common cold and/or acne.

SOURCE – Apotex.

REFERENCES

1. Karimian, K. et al. (Apotex Inc.) *Thiadiazole cpds. useful as inhibitors of cysteine activity dependent enzymes*. WO 9945027.

ISIS-13989

281116

Phosphorothioate 2'-deoxyoligonucleotide whose sequence is: 5'-GGATACGCCATGCACCTTCA-3'

ACTION – Antisense phosphorothioate oligonucleotide for modulating the expression of platelet endothelial cell adhesion molecule-1 (PECAM-1), potentially useful in the treatment and diagnosis of PECAM-1-mediated disorders such as inflammation, autoimmune diseases and cancer. *In vitro*, it produced 53.1 and 66.6% inhibition of PECAM-1 expression in murine bEND.3 cells at 75 and 300 nM, respectively. *In vivo*, it dose-dependently (0.3-30 mg/kg/day i.v. x 7 days) reduced the transmigration of polymorphonuclear neutrophil granulocytes into the peritoneal fluid of lipopolysaccharide-challenged mice. Another preferred antisense oligonucleotide is:

Phosphorothioate oligonucleotide whose sequence is: 5'-TCCTTCCAGGGATGTGCATC-3', in which all the C residues are 5-methylcytosines and all residues are 2'-deoxy, except residues T, G, T, G, A and T in positions 13, 14, 15, 16, 18 and 19, which are 2'-methoxyethoxy-substituted

ISIS-17561 [281117]

SOURCE – Isis Pharmaceuticals.

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.) *Antisense modulation of PECAM-1*. US 5955443, WO 9947708.

PEG-sTNF-RI

280303

Recombinant form of the high-affinity p55 soluble tumor necrosis factor receptor type I (sTNF-RI) to which a 30-kD polyethylene glycol (PEG) molecule is attached

Pegylated soluble tumor necrosis factor receptor type I

ACTION – TNF- α inhibitor, a recombinant soluble TNF receptor type I linked to polyethylene glycol with significant efficacy in rat models of arthritis as regards inflammation and bone resorption, both alone and in combination with anakinra (IL-1ra) or dexamethasone, the combinations showing additive or even synergistic effects. Experimental evidence also indicates potential for preventing the development of experimental autoimmune encephalomyelitis in mice, a model of multiple sclerosis, by interfering with the expression of adhesion molecules such as VCAM-1 in the CNS. Phase I clinical trials showed good tolerance, no immunogenicity and a favorable pharmacokinetic profile, with potential for infrequent dosing. Currently in phase II clinical trials for the treatment of rheumatoid arthritis.

SOURCE – Amgen.

REFERENCES

1. Bende, A.M. et al. *Combination benefit of PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI) and dexamethasone or indomethacin in adjuvant arthritic rats*. *Inflamm Res* 1999, 48(8): 453.

2. Bende, A.M. et al. *Combination benefit of treatment with recombinant human interleukin-1 receptor antagonist (IL-1ra) and pegylated recombinant human soluble tumor necrosis factor receptor type I (PEG sTNF-RI) in animal models of rheumatoid arthritis*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 602.

3. Bende, A.M. et al. *Effects of PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI) alone and in combination with methotrexate in adjuvant arthritic rats*. *Clin Exp Rheumatol* 1999, 17(5): 553.

4. Caldwell, J.R. et al. *A phase I study of pegylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI[55]) in subjects with rheumatoid arthritis (RA)*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 993.

5. Davis, M.W. et al. *Non-immunogenicity of a regylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI [55])*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 37.

6. Edwards, C.K. et al. *Clinical and histopathological characterization of arthritis in male and female tumor necrosis factor- α knockout (TNF- α -I-) and membrane-bound TNF- α transgenic (TNF- α Tg86) mice injected with Mycoplasma pulmonis or Mycoplasma arthritidis*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 296.

7. Feige, U. et al. *Combining anti-IL-1 and anti-TNF treatments provides better efficacy in rat adjuvant arthritis than does either agent alone*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 1875.

8. Martin, S.W. et al. *The pharmacokinetics of subcutaneous injections of pegylated recombinant methionyl soluble tumor necrosis factor-type I receptor (PEG sTNF-RI) in subjects with active rheumatoid arthritis*. 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 50.

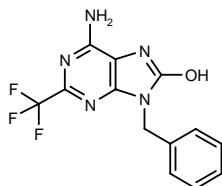
9. Selmai, K.W. et al. *Effect of PEG-sTNF-RI on immune mechanisms involved in prevention of EAE*. *Eur Cytokine Netw* 1996, 7(2): Abst 244.

IMMUNOMODULATING AGENTS

280460

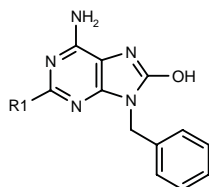
6-Amino-9-benzyl-2-(trifluoromethyl)-9H-purin-8-ol

9-Benzyl-8-hydroxy-2-(trifluoromethyl)adenine



C13 H10 F3 N5 O; Mol wt: 309.2500

ACTION – Immunomodulating agent shown to stimulate the production of interferon alfa, interferon gamma and TNF- α *in vitro* at 0.1-10 μ M and *ex vivo* in mice at 30 mg/kg p.o., and to reduce the antigen-stimulated production of IL-5 and IL-4 in murine spleen cells at 0.1-10 μ M. In addition, compound produced 52.3% inhibition of antigen-stimulated eosinophil infiltration in sensitized mice at 30 mg/kg p.o. vs. 18.9% inhibition at 3 mg/kg for dexamethasone. Potentially useful in the treatment of allergic and viral diseases and cancer. Other compounds from this series of adenine derivatives include the following:



Compound	R1	Formula
280462	CF ₂ CF ₃	C ₁₄ H ₁₀ F ₅ N ₅ O
280463	Cl	C ₁₂ H ₁₀ ClN ₅ O

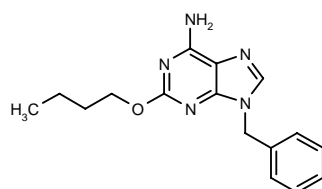
SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

REFERENCES

1. Isobe, Y. et al. (Japan Energy Corp.; Sumitomo Pharmaceuticals Co., Ltd.) *Novel adenine derivs. and their medicinal use*. JP 99180982.

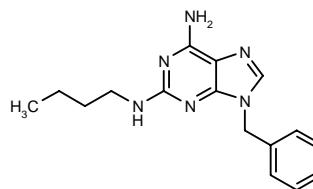
280522

9-Benzyl-2-butoxyadenine



C16 H19 N5 O; Mol wt: 297.3601

ACTION – Immunomodulating, antiviral and antineoplastic agent that induces interferon biosynthesis, as demonstrated in murine spleen cells challenged with bovine vesicular stomatitis virus. Another heterocyclic compound is:



280523: C16 H20 N6

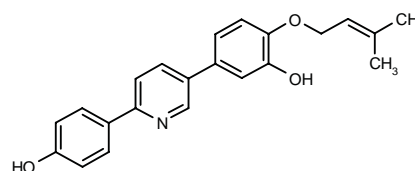
SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

REFERENCES

1. Kurimoto, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.; Japan Energy Corp.) *Heterocyclic derivs.* JP 99180981.

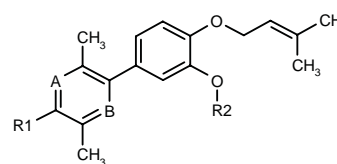
280793

5-[6-(4-Hydroxyphenyl)pyridin-3-yl]-2-(3-methylbut-2-enyloxy)phenol

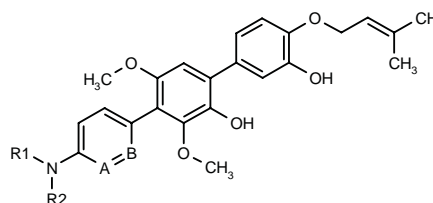


C22 H21 N O3; Mol wt: 347.4119

ACTION – Immunosuppressive and antiallergic agent shown to inhibit the mitogenic response of concanavalin A- and lipopolysaccharide-stimulated murine spleen cells with IC₅₀ values of 10 ng/ml or less. In addition, it was shown to inhibit the proliferation of murine lymphoma EL4 cells with an IC₅₀ value of 33 ng/ml. Other tricyclic compounds include the following:



Compound	R1	R2	A	B	Formula
280794	4-OH-Ph	H	CH	N	C ₂₄ H ₂₅ NO ₃
280795	4-OH-Ph	H	N	CH	C ₂₄ H ₂₅ NO ₃
280799	4-N(Me)2-PhO	Me	CH	CH	C ₂₈ H ₃₃ NO ₃



Compound	R1	R2	A	B	Formula
280796	CH ₂ CH=C(Me) ₂	H	CH	N	C ₂₉ H ₃₄ N ₂ O ₅
280797	Me	Me	CH	N	C ₂₆ H ₃₀ N ₂ O ₅
280798	Me	Me	N	CH	C ₂₆ H ₃₀ N ₂ O ₅

Compounds of the invention are also able to inhibit the production of IgE antibody, as demonstrated in ovalbumin-sensitized mice.

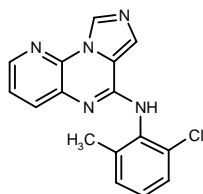
SOURCE – Shionogi.

REFERENCES

1. Tanimoto, N. et al. (Shionogi & Co. Ltd.) *Novel tricyclic cpd.* WO 9938829.

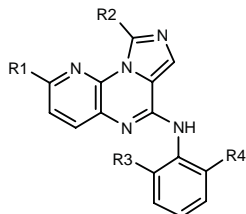
281121

N-(2-Chloro-6-methylphenyl)imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazin-6-amine

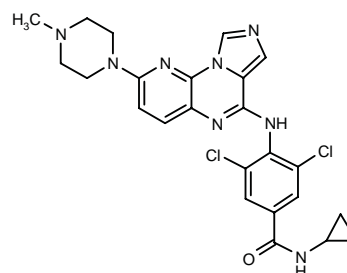


C16 H12 Cl N5; Mol wt: 309.7588

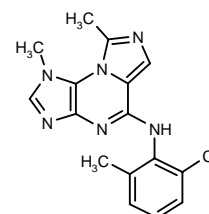
ACTION – An inhibitor of protein tyrosine kinases, particularly Src family kinases such as Lck, Fyn, Src, Yes, Hck, Fgr and Blk, with potential in the treatment of a broad range of disorders including transplant rejection, graft-versus-host disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, T-cell-mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barré syndrome, chronic obstructive pulmonary disease, dermatitis, asthma, allergic rhinitis, ischemia–reperfusion injury and cancer. Other specifically claimed compounds within this series of heterocyclo-substituted imidazopyrazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
281122	4-(1-Pip)-1-Pip	H	Cl	Me	C ₂₆ H ₃₀ ClN ₇
281125	4-(CH ₂ CH ₂ OH)-1-Piz	H	Cl	F	C ₂₁ H ₂₁ ClFN ₇ O
281126	4-Me-perhydro-1,4-diazepin-1-yl	H	Me	Me	C ₂₃ H ₂₇ N ₇
281127	NHCH(CH ₂ OH) ₂	H	F	Cl	C ₁₈ H ₁₆ ClFN ₆ O ₂
281128	N(Me)CH ₂ -CH ₂ NHMe	H	Cl	Me	C ₂₀ H ₂₂ ClN ₇
281129	H	i-Pr-NHCONH	Me	Me	C ₂₁ H ₂₃ N ₇ O



281123: C24 H24 Cl2 N8 O



281124: C16 H15 Cl N6

SOURCE – Bristol-Myers Squibb.

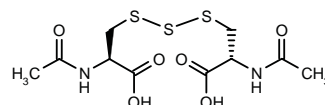
REFERENCES

1. Chen, P. et al. (Bristol-Myers Squibb Co.) *Heterocyclo-substd. imidazopyrazine protein tyrosine kinase inhibitors.* US 5990109, WO 9945009.

281335

(*R,R'*)-3,3'-Trithiobis(2-acetamidopropionic acid)

Bis(*N*-acetyl-L-cysteine) trisulfide



C10 H16 N2 O6 S3; Mol wt: 356.4424

ACTION – Immunostimulating and antiarteriosclerotic agent, a representative compound from a series of trisulfide analogues of *N*-acetyl-L-cysteine.

SOURCE – AstraZeneca.

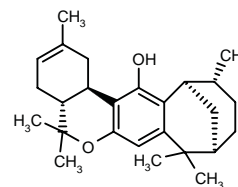
REFERENCES

1. Bergstrand, H. et al. (Astra AB) *New cpds.* WO 9948865.

AM-724

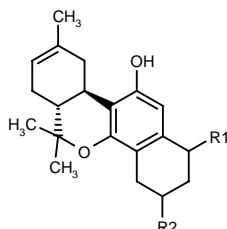
283127

(4*aR*,9*R*,12*R*,13*R*,14*bR*)-2,5,5,8,8,12-Hexamethyl-4,4*a*,5,8,9,10,11,12,13,14*b*-decahydro-1*H*-9,13-methano-benzo[*d*]cyclohepta[4,5]benzo[1,2-*b*]pyran-14-ol

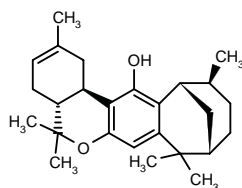


C26 H36 O2; Mol wt: 380.5684

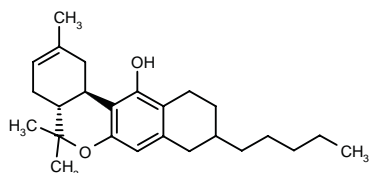
ACTION – Immunosuppressant that selectively activates the cannabinoid CB₂ receptor and is therefore expected to be devoid of the psychotropic and sedative side effects characteristic of cannabinoids such as Δ⁸-tetrahydrocannabinol. It has about 400 times higher affinity for the CB₂ receptor (K_i = 16.9 nM) than for the CB₁ receptor (K_i = 6877 nM). Potentially useful for suppressing organ transplant rejection, for treating autoimmune diseases (e.g., lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases), for treating inflammation and for suppressing peripheral and idiopathic pain. Other representative cannabinoids from this series are:



Compound	R1	R2	Formula
AM-855 [283132]	H	C ₆ H ₁₃	C ₂₆ H ₃₆ O ₂
AM-858 [283133]	C ₆ H ₁₃	H	C ₂₆ H ₃₆ O ₂



AM-725 [283128]: C₂₆ H₃₆ O₂



AM-856 [283131]: C₂₅ H₃₆ O₂

SOURCE – University of Connecticut, Storrs, CT (US).

REFERENCES

1. Makriyannis, A. et al. (University of Connecticut) *Cannabinoids selective for the CB₂ receptor*. WO 9957107.

HEPATYRIX

277946

Combined hepatitis A and typhoid vaccine

ACTION – Combined inactivated hepatitis A and purified Vi polysaccharide typhoid vaccine.

INDICATION – Active immunization against hepatitis A virus infection and typhoid fever in adults and adolescents at least 15 years of age.

PRESENTATION – Prefilled syringes (1 ml) containing 25 µg Vi polysaccharide of *Salmonella typhi* and not less than 1440 ELISA units of inactivated hepatitis A viral antigen.

PROPRIETARY NAME – *Hepatyrix* (GB).

SOURCE – SmithKline Beecham.

REFERENCES

1. De Clerq, N.A. et al. *A combined Vi polysaccharide typhoid and inactivated hepatitis A vaccine: Immunogenicity follow-up*. 37th Annu Meet Infect Dis Soc Am (Nov 18-21, Philadelphia) 1999, Abst 641.
2. *SmithKline Beecham launches new combined vaccine for hepatitis A and typhoid in the U.K.* DailyDrugNews.com (Daily Essentials) 1999, June 30.

ISIS-16374

281291

Phosphorothioate oligonucleotide whose sequence is: 5'-TGAGGCTACCTGACACAGTG-3', in which all residues are 2'-deoxy, except residues T, G, A, G, G, A, G, T and G in positions 1, 2, 3, 4, 5, 17, 18, 19 and 20, which are 2'-methoxyethoxy-substituted, and C in position 16 is 2'-methoxyethoxy-5-methylcytosine

ACTION – Antisense oligonucleotide for modulating the expression of lymphocyte function-associated antigen 3 (LFA-3; also known as CD58) protein. Compound produced 46.7 and 53.3% inhibition of human LFA-3 expression and protein activity at a concentration of 10 nM in HUVEC (human umbilical vein endothelial cells). Compound was shown to inhibit costimulation of cytokine production from phytohemagglutinin-activated CD4⁺ T-cells in HUVEC, being nearly as effective as antibodies to LFA-3 or CD2. In addition, pretreatment of HUVEC with test compound inhibited the production of IL-2 and interferon gamma by allogeneic CD4⁺ T-cells. Potentially useful in the treatment of inflammation, inflammatory bowel disease, allograft rejection, graft-versus-host disease, arthritis, autoimmune diseases and hyperproliferative disorders. Other preferred antisense oligonucleotides are:

Phosphorothioate oligonucleotide whose sequence is: 5'-CCGCGTCGCTCCCAGCAACC-3', in which all residues are 2'-deoxy, except residues G, G, A and A in positions 3, 5, 17 and 18, which are 2'-methoxyethoxy-substituted, and C in positions 1, 2, 4, 16, 19 and 20 are 2'-methoxyethoxy-5-methylcytosines

ISIS-16371 [281292]

Phosphorothioate oligonucleotide whose sequence is: 5'-CCGCGTCGCTCCCAGCAACC-3', in which all residues are 2'-deoxy, except residues G, G, T, A and A in positions 3, 5, 6, 17 and 18, which are 2'-methoxyethoxy-substituted, and C in positions 1, 2, 4, 7, 16, 19 and 20 are 2'-methoxyethoxy-5-methylcytosine

ISIS-16910 [281293]

Mixed phosphodiester/phosphorothioate oligonucleotide whose sequence is: 5'-TGAGGCTACCTGACACAGTC-3', in which all linkages are phosphorothioate except between residues 1-2, 2-3, 3-4, 4-5, 16-17, 17-18, 18-19 and 19-20 which are phosphodiester, all residues are 2'-deoxy, except residues T, G, A, G, G, A, G, T and G in positions 1, 2, 3, 4, 5, 17, 18, 19 and 20, which are 2'-methoxyethoxy-substituted, and C in position 16 is 2'-methoxyethoxy-5-methylcytosine

ISIS-17159 [281294]

SOURCES – Isis Pharmaceuticals; Yale University, New Haven, CT (US).

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.; Yale University) *Antisense modulation of LFA-3*. WO 9947707.

15.9D5 MAb

280923

Anti-T-cell receptor (TCR) $\alpha\beta$ monoclonal antibody

ACTION – Immunosuppressant, a monoclonal antibody to the T-cell receptor (TCR) $\alpha\beta$, able to inhibit mixed leukocyte cultures *in vitro* without mitogenic properties in soluble or immobilized form. In dogs, compound prevented rejection of allogeneic marrow grafts in animals conditioned with a suboptimal dose of total-body irradiation (TBI) and was well tolerated. Potentially useful for the prevention of bone marrow graft rejection.

SOURCES – Fred Hutchinson Cancer Research Center, Seattle, WA (US); University of Washington, Seattle, WA (US).

REFERENCES

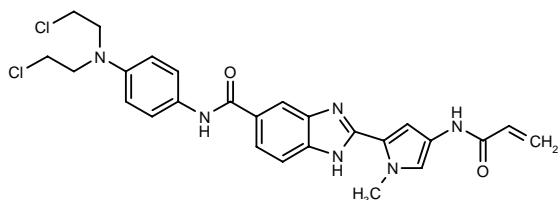
1. Barsoukov, A.A. et al. *The use of an anti-TCR $\alpha\beta$ monoclonal antibody to control host-versus-graft reactions in canine marrow allograft recipients conditioned with low dose total body irradiation*. Transplantation 1999, 67(10): 1329.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

280541

N-[4-[*N,N*-Bis(2-chloroethyl)amino]phenyl]-2-(4-propenamido-1-methyl-1*H*-pyrrol-2-yl)-1*H*-benzimidazole-5-carboxamide



C26 H26 Cl2 N6 O2; Mol wt: 525.4374

ACTION – Antineoplastic agent that binds to DNA, proven active *in vitro* against murine melanoma B16 cells (IC₅₀ = 0.22 μ g/ml).

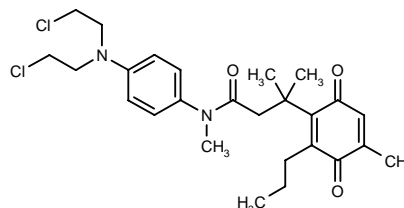
SOURCE – Mitsui Chemicals.

REFERENCES

1. Matsunaga, A. et al. (Mitsui Chemicals, Inc.) *Pyrrolyl benzimidazole derivs. having side chain of acrylic acid derivs*. JP 99189594.

281337

N-[4-[Bis(2-chloroethyl)amino]phenyl]-*N*,3-dimethyl-3-(5-methyl-3-propyl-1,4-benzoquinon-2-yl)butyramide



C26 H34 Cl2 N2 O3; Mol wt: 493.4716

ACTION – Antineoplastic agent, a representative compound from a series of hypoxia-selective double-prodrug quinone derivatives designed to rapidly break down to release a cytotoxic nitrogen mustard upon reduction to the hydroquinone form in a hypoxic region of a tumor mass; the cytotoxic agent, once released, can also diffuse into nearby oxic regions to continue the destruction of cancer cells. Compound was shown to inhibit the growth of spheroidal aggregates of murine breast cancer EMT6 cells in an oxygenated culture medium, with a stasis EC₅₀ value of about 4 μ M. When tested *in vivo* in mice bearing murine breast T18 tumors, it was shown to delay tumor growth by about 9 days following a single i.p. administration of 20 mg/kg.

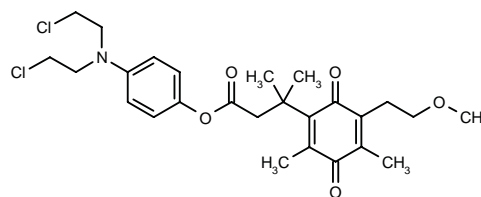
SOURCE – AstraZeneca.

REFERENCES

1. Boyle, F.T. (Zeneca Ltd.) *Anti-tumour agents*. WO 9948860.

281338

3-[3,5-Dimethyl-6-(2-methoxyethyl)-1,4-benzoquinon-2-yl]-3-methylbutyric acid 4-[bis(2-chloroethyl)amino]phenyl ester



C26 H33 Cl2 N O5; Mol wt: 510.4547

ACTION – Antineoplastic agent, a representative compound from a series of hypoxia-selective double-prodrug quinone derivatives designed to rapidly break down to release a cytotoxic nitrogen mustard upon reduction to the hydroquinone form in a hypoxic region of a tumor mass; the cytotoxic agent, once released, is also able to diffuse into nearby oxic regions to continue the destruction of cancer cells. *In vitro*, compound exhibited an IC₅₀ value of 4.8 μ M against the growth of murine breast cancer T18 cells under oxic conditions and was shown to inhibit the growth of spheroidal aggregates of murine breast cancer EMT6 cells in an oxygenated culture medium, with a stasis EC₅₀ value of about 6 μ M. When tested *in vivo* in mice bearing murine breast T18 tumors, it was shown to delay tumor growth by about 12 days following a single i.p. administration of 50 mg/kg.

SOURCES – Isis Pharmaceuticals; Yale University, New Haven, CT (US).

REFERENCES

1. Bennett, C.F. et al. (Isis Pharmaceuticals, Inc.; Yale University) *Antisense modulation of LFA-3*. WO 9947707.

15.9D5 MAb

280923

Anti-T-cell receptor (TCR) $\alpha\beta$ monoclonal antibody

ACTION – Immunosuppressant, a monoclonal antibody to the T-cell receptor (TCR) $\alpha\beta$, able to inhibit mixed leukocyte cultures *in vitro* without mitogenic properties in soluble or immobilized form. In dogs, compound prevented rejection of allogeneic marrow grafts in animals conditioned with a suboptimal dose of total-body irradiation (TBI) and was well tolerated. Potentially useful for the prevention of bone marrow graft rejection.

SOURCES – Fred Hutchinson Cancer Research Center, Seattle, WA (US); University of Washington, Seattle, WA (US).

REFERENCES

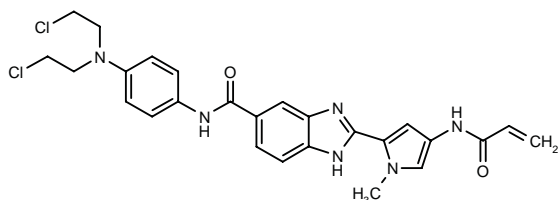
1. Barsoukov, A.A. et al. *The use of an anti-TCR $\alpha\beta$ monoclonal antibody to control host-versus-graft reactions in canine marrow allograft recipients conditioned with low dose total body irradiation*. Transplantation 1999, 67(10): 1329.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

280541

N-[4-[*N,N*-Bis(2-chloroethyl)amino]phenyl]-2-(4-propenamido-1-methyl-1*H*-pyrrol-2-yl)-1*H*-benzimidazole-5-carboxamide



C26 H26 Cl2 N6 O2; Mol wt: 525.4374

ACTION – Antineoplastic agent that binds to DNA, proven active *in vitro* against murine melanoma B16 cells (IC₅₀ = 0.22 μ g/ml).

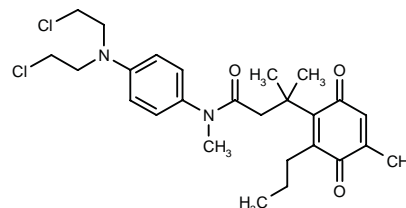
SOURCE – Mitsui Chemicals.

REFERENCES

1. Matsunaga, A. et al. (Mitsui Chemicals, Inc.) *Pyrrolyl benzimidazole derivs. having side chain of acrylic acid derivs*. JP 99189594.

281337

N-[4-[Bis(2-chloroethyl)amino]phenyl]-*N*,3-dimethyl-3-(5-methyl-3-propyl-1,4-benzoquinon-2-yl)butyramide



C26 H34 Cl2 N2 O3; Mol wt: 493.4716

ACTION – Antineoplastic agent, a representative compound from a series of hypoxia-selective double-prodrug quinone derivatives designed to rapidly break down to release a cytotoxic nitrogen mustard upon reduction to the hydroquinone form in a hypoxic region of a tumor mass; the cytotoxic agent, once released, can also diffuse into nearby oxic regions to continue the destruction of cancer cells. Compound was shown to inhibit the growth of spheroidal aggregates of murine breast cancer EMT6 cells in an oxygenated culture medium, with a stasis EC₅₀ value of about 4 μ M. When tested *in vivo* in mice bearing murine breast T18 tumors, it was shown to delay tumor growth by about 9 days following a single i.p. administration of 20 mg/kg.

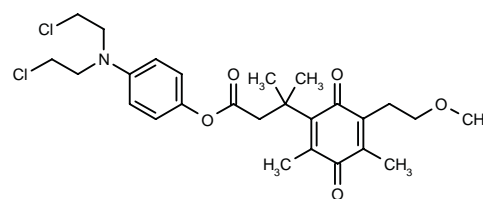
SOURCE – AstraZeneca.

REFERENCES

1. Boyle, F.T. (Zeneca Ltd.) *Anti-tumour agents*. WO 9948860.

281338

3-[3,5-Dimethyl-6-(2-methoxyethyl)-1,4-benzoquinon-2-yl]-3-methylbutyric acid 4-[bis(2-chloroethyl)amino]phenyl ester



C26 H33 Cl2 N O5; Mol wt: 510.4547

ACTION – Antineoplastic agent, a representative compound from a series of hypoxia-selective double-prodrug quinone derivatives designed to rapidly break down to release a cytotoxic nitrogen mustard upon reduction to the hydroquinone form in a hypoxic region of a tumor mass; the cytotoxic agent, once released, is also able to diffuse into nearby oxic regions to continue the destruction of cancer cells. *In vitro*, compound exhibited an IC₅₀ value of 4.8 μ M against the growth of murine breast cancer T18 cells under oxic conditions and was shown to inhibit the growth of spheroidal aggregates of murine breast cancer EMT6 cells in an oxygenated culture medium, with a stasis EC₅₀ value of about 6 μ M. When tested *in vivo* in mice bearing murine breast T18 tumors, it was shown to delay tumor growth by about 12 days following a single i.p. administration of 50 mg/kg.

SOURCE – AstraZeneca.

REFERENCES

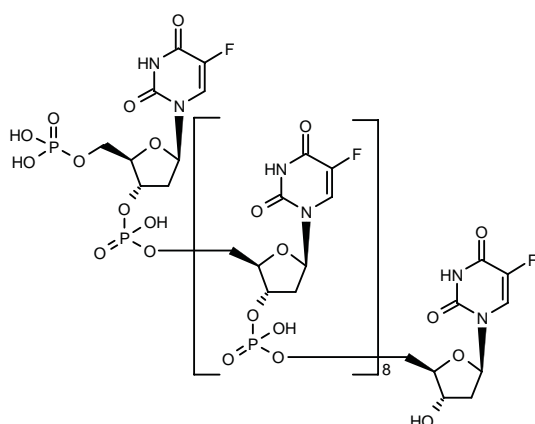
- Boyle, F.T. (Zeneca Ltd.) *Anti-tumour agents*. WO 9948857.

ANTIMETABOLITES

FdUMP[10]

280223

10-Mer oligodeoxynucleotide containing only the nucleoside 2'-deoxy-5-fluorouridine-5'-*O*-monophosphate



C90 H102 F10 N20 O71 P10; Mol wt: 3099.5850

ACTION – Antineoplastic agent, an oligodeoxynucleotide having 5-FU as the only nucleobase that acts as an inhibitor of thymidylate synthase (TS), with markedly improved activity relative to 5-FU (> 100-fold) in inhibiting clonogenic survival of human colorectal tumor H630 cells following long exposure times. H630-10 cells overexpressing TS and resistant to 5-FU remained sensitive to compound. It was also active against numerous tumor cell lines including non-small cell lung cancer, melanoma, ovarian cancer and renal cancer cells. *In vivo*, compound was better tolerated than 5-FU, no deaths being observed after doses of 200 mg/kg/day x 3.

SOURCES – University of Calgary, Calgary, AB (CA); University of Nebraska, Omaha, NE (US).

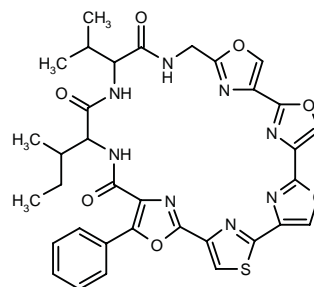
REFERENCES

- Gmeiner, W.H. et al. *Cytotoxicity and in-vivo tolerance of FdUMP[10]: A novel pro-drug of the TS inhibitory nucleotide FdUMP*. Nucleosides Nucleotides 1999, 18(6-7): 1729.
- Gmeiner, W.H. et al. *Positive interaction between 5-fluorouracil and FdUMP[10] in the inhibition of human colorectal tumor cell proliferation*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 457.

ANTIBIOTICS AND ALKALOIDS

280502

23-Isopropyl-20-(1-methylpropyl)-16-phenyl-3,7,15,28-tetraoxa-11-thia-19,22,25,30,31,32,33,34-octaaza-hexacyclo[25.2.1.1^{2,5}.1^{6,9}.1^{10,13}.1^{14,17}]tetratriaconta-1(29),2(34),4,6(33),8,10(32),12,14(31),16,27(30)-decaene-18,21,24-trione



C34 H32 N8 O7 S; Mol wt: 696.7418

ACTION – Antineoplastic agent isolated from the micro-organism *Streptomyces nobilis* JCM4274 with potent antiproliferative activity against HeLa S3 cells (IC₅₀ = 14 nM).

SOURCE – Yamanouchi.

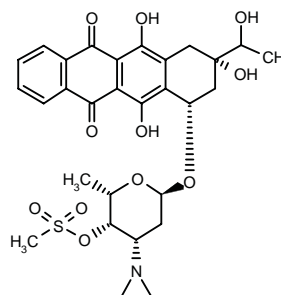
REFERENCES

- Hayata, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel antitumor cpds*. JP 99180997.

281876

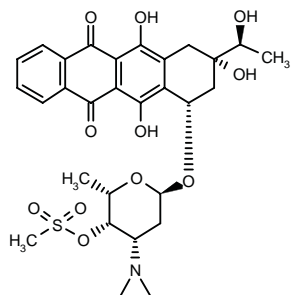
(±)-7(*S*)-[3-Aziridinyl-4-*O*-(methylsulfonyl)-2,3,6-trideoxy-α-*L*-lyxo-hexopyranosyloxy]-9(*S*)-(1-hydroxyethyl)-6,9,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione

(±)-3'-Aziridinyl-9-deacetyl-3'-deamino-4-demethoxy-9-(1-hydroxyethyl)-4'-*O*-(methylsulfonyl)daunorubicin



C29 H33 N O11 S; Mol wt: 603.6417

ACTION – Antineoplastic anthracycline glycoside with potent *in vitro* cytotoxicity against murine leukemia L1210, Jurkat, CEM and colon adenocarcinoma LoVo cells ($IC_{50} = 3.76 \pm 0.13$, 4.87 ± 0.7 , 5.86 ± 0.4 and 20.3 ± 2 ng/ml, respectively). *In vivo*, the compound increased the life span of mice bearing disseminated doxorubicin-resistant P388/DX leukemia, with ILS% values of 80 and 102 at doses of 2.9 and 3.8 mg/kg i.v., respectively. The *S*-isomer is reported to be particularly preferred:



282878: C₂₉ H₃₃ N O₁₁ S

SOURCE – Pharmacia & Upjohn.

REFERENCES

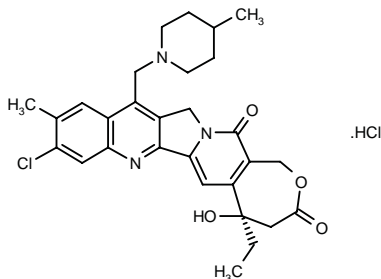
1. Geroni, C. et al. (Pharmacia & Upjohn SpA) *13-Dihydro-3'aziridino anthracyclines*. WO 9952921.

DNA-INTERCALATING DRUGS

BN-80927*^{1,5}

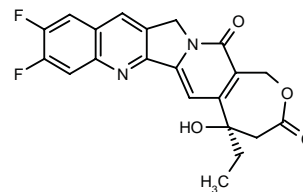
275177

(+)-9-Chloro-5(*R*)-ethyl-5-hydroxy-10-methyl-12-(4-methylpiperidin-1-ylmethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione hydrochloride



C₂₉ H₃₂ Cl N₃ O₄ . HCl; Mol wt: 558.5027

ACTION – Antineoplastic agent, a dual inhibitor of topoisomerase type I and II with marked antitumor activity against several human tumor cell lines including colon adenocarcinoma HT-29 ($IC_{50} = 6.66$ nM), ovarian carcinoma SKOV-3 ($IC_{50} = 13$ nM), prostate carcinoma DU 145 ($IC_{50} = 3$ nM) and breast carcinoma MCF-7 ($IC_{50} = 48$ nM); the cytotoxicity of compound was superior to that of DACA or intoplicine, two dual topoisomerase I and II inhibitors currently in clinical trials. Experimental evidence indicated that compound acts as a potent topoisomerase I poison and a catalytic inhibitor of topoisomerase II. Another related homocamptothecin derivative is:



BN-80915 [275176]:**,¹⁻⁸ C₂₁ H₁₆ F₂ N₂ O₄

SOURCE – Institut Henri Beaufour.

REFERENCES

1. Cazaux, J.-B. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Optically pure camptothecin analogues, optically pure synthesis intermediate and method for preparing same*. FR 2768431, WO 9911646.
2. Celma, C. et al. *Biotransformation of 14C-BN80915, a novel E-ring modified topoisomerase I inhibitor, after single dose administration in rats*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 540.
3. Kasprzyk, P.G. et al. *An E-ring modified camptothecin, BN-80915, shows unusual stability and high activity both in vitro and in vivo*. Proc Amer Assoc Cancer Res 1999, 40 Abst 739.
4. Larsen, A.K. et al. *Unusual potency of BN 80915, a novel E-ring modified camptothecin, towards human colon adenocarcinoma cells*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 665.
5. Lavergne, O. et al. *BN 80927: A novel homocamptothecin with inhibitory activities on both topoisomerase I and topoisomerase II*. Bioorg Med Chem Lett 1999, 9(17): 2599.
6. Menargues, A. et al. *Pharmacokinetics and oral bioavailability of BN80915, a novel topoisomerase I inhibitor, after single dose administration in rats*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 552.
7. Principe, P. et al. *Anti-tumour profile of BN80915, a novel E-ring modified topoisomerase I inhibitor*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 664.
8. Pruñonosa, J. et al. *Dog pharmacokinetics and oral bioavailability of BN80915, a novel topoisomerase I inhibitor*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 539.

*Identified compound **275177** (see **275176**) Drug Data Rep 1999, 021(05): 0450.

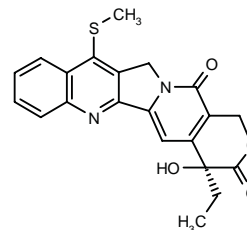
Identified compound **275176 Drug Data Rep 1999, 021(05): 0450.

BNP-1100

278815

4(*S*)-Ethyl-4-hydroxy-11-(methylsulfanyl)-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione

7-(Methylsulfanyl)camptothecin



C₂₁ H₁₈ N₂ O₄ S; Mol wt: 394.4492

ACTION – Antineoplastic agent, an inhibitor of topoisomerase I proven to exert highly lethal effects *in vitro* against human colorectal cancer HCT-8 cells when given in combination with an inhibitor of thymidylate synthase (ZD-1694). Compound also exhibits subnanomolar potency *in vitro* against various human solid tumors including prostate, pancreas, colon, lung, breast and ovarian tumors and melanoma.

SOURCE – BioNumerik.

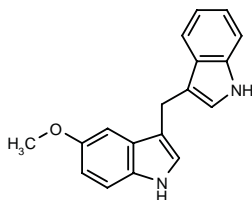
REFERENCES

1. Hausheer, F.H. et al. (BioNumerik Pharmaceuticals, Inc.) *Highly lipophilic camptothecin derivs.* WO 9807727.
2. Hausheer, F.H. et al. (BioNumerik Pharmaceuticals, Inc.) *Highly lipophilic camptothecin derivs.* WO 9835940.
3. Hausheer, F. et al. *Karenitecins: A novel, potent class of oral highly lipophilic topo I inhibitors.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1526.
4. Matsui, S.I. et al. *Characterisation of a synergistic interaction between a thymidylate synthase inhibitor, ZD1694, and a novel lipophilic topoisomerase I inhibitor karenitecin, BNP1100: Mechanisms and clinical implications.* Eur J Cancer 1999, 35(6): 984.

HORMONAL AGENTS

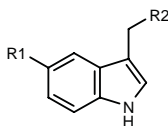
280690

3-(1*H*-Indol-3-ylmethyl)-5-methoxy-1*H*-indole



C₁₈ H₁₆ N₂ O; Mol wt: 276.3374

ACTION – Antiestrogenic agent with potential in the treatment of estrogen-dependent tumors, particularly breast and endometrial cancer. Compound was found to concentration-dependently inhibit the estrogen-induced growth of human breast cancer MCF-7 cells *in vitro* and was also shown to be effective in inhibiting the growth of DMBA-induced mammary tumors in rats at 5 mg/kg i.p. every 2 days, a dose level reported to be relatively low compared to that of tamoxifen in this model. Other compounds from this series of indole-3-carbinol and diindolymethane derivatives include the following:



Compound	R1	R2	Formula
280691	F	3-indolyl	C ₁₇ H ₁₃ FN ₂
280692	NO ₂	OH	C ₉ H ₈ N ₂ O ₃
280693	Br	3-indolyl	C ₁₇ H ₁₃ BrN ₂

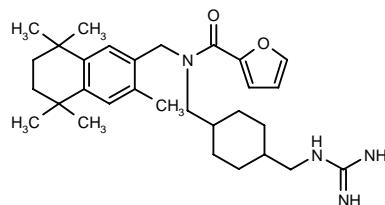
SOURCE – Texas A&M University, College Station, TX (US).

REFERENCES

1. Safe, S.H. (Texas A&M University) *Indole-3-carbinol, diindolymethane and subst. analogs as antiestrogens.* US 5948808.

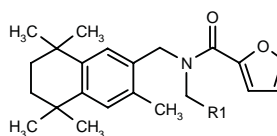
281137

N-[4-(Guanidinomethyl)cyclohexylmethyl]-*N*-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylmethyl)furan-2-carboxamide

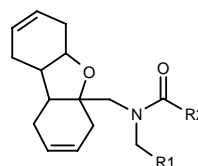


C₃₀ H₄₄ N₄ O₂; Mol wt: 492.7036

ACTION – Agent for the treatment of sex hormone-dependent disorders and for controlling fertility that displays potent gonadotropin-releasing hormone (GnRH)-antagonist activity. Other specifically claimed compounds include the following:



Compound	R1	Formula
281138	3-[NH ₂ C(=NH)NHCH ₂]-cyclohexyl	C ₃₀ H ₄₄ N ₄ O ₂
281139	4-[NH ₂ C(=NH)NHCH ₂]-Ph	C ₃₀ H ₃₈ N ₄ O ₂
281140	3-[NH ₂ C(=NH)NHCH ₂]-Ph	C ₃₀ H ₃₈ N ₄ O ₂
281141	(CH ₂) ₃ NHC(=NH)NH ₂	C ₂₆ H ₃₈ N ₄ O ₂



Compound	R1	R2	Formula
281142	3-[NH ₂ C(=NH)NHCH ₂]-cyclohexyl	1-Naph	C ₃₃ H ₄₂ N ₄ O ₂
281143	(CH ₂) ₃ NHC(=NH)NH ₂	1-Naph	C ₂₉ H ₃₆ N ₄ O ₂
281144	4-[NH ₂ C(=NH)NHCH ₂]-Ph	1-Naph	C ₃₃ H ₃₆ N ₄ O ₂
281145	(CH ₂) ₃ NHC(=NH)NH ₂	2-Naph	C ₂₉ H ₃₆ N ₄ O ₂
281146	3-[NH ₂ C(=NH)NHCH ₂]-cyclohexyl	2-Naph	C ₃₃ H ₄₂ N ₄ O ₂
281147	4-[NH ₂ C(=NH)NHCH ₂]-Ph	2-Naph	C ₃₃ H ₃₆ N ₄ O ₂

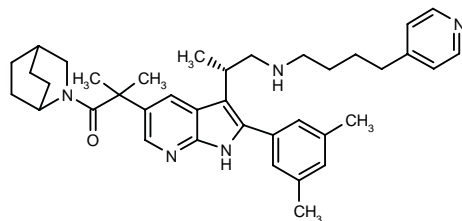
SOURCE – Alanex.

REFERENCES

1. Anderson, M. et al. (Alanex Corp.) *Non-peptide GnRH agents.* WO 9944987.

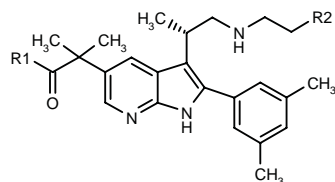
281714

1-(2-Azabicyclo[2.2.2]oct-2-yl)-2-[2-(3,5-dimethylphenyl)-3-[1(S)-methyl-2-[4-(4-pyridinyl)butylamino]ethyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methylpropan-1-one



C38 H49 N5 O; Mol wt: 591.8391

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	R1	R2	Formula
281715	2-azabicyclo[2.2.2]oct-2-yl	4-Pyr-CH2	C ₃₇ H ₄₇ N ₅ O
281716	2-azabicyclo[2.2.2]oct-2-yl	1-Me-6-oxo-1,6-dihydro-3-Pyr	C ₃₇ H ₄₇ N ₅ O ₂
281717	2-azabicyclo[2.2.2]oct-2-yl	4-Pyr	C ₃₆ H ₄₅ N ₅ O
281718	2-azabicyclo[2.2.2]oct-2-yl	2-Me-1-oxido-4-Pyr	C ₃₇ H ₄₇ N ₅ O ₂
281719	2-azabicyclo[2.2.2]oct-2-yl	5-benzotriazolyl	C ₃₇ H ₄₅ N ₇ O
281720	7-azabicyclo[2.2.1]hept-7-yl	4-Pyr-CH2	C ₃₆ H ₄₅ N ₅ O
281721	7-azabicyclo[2.2.1]hept-7-yl	4-Pyr	C ₃₅ H ₄₃ N ₅ O
281722	7-azabicyclo[2.2.1]hept-7-yl	2-Me-1-oxido-4-Pyr	C ₃₆ H ₄₅ N ₅ O ₂
281723	7-azabicyclo[2.2.1]hept-7-yl	5-benzotriazolyl	C ₃₆ H ₄₃ N ₇ O
281724	7-azabicyclo[2.2.1]hept-7-yl	1-Me-6-oxo-1,6-dihydro-3-Pyr	C ₃₆ H ₄₅ N ₅ O ₂

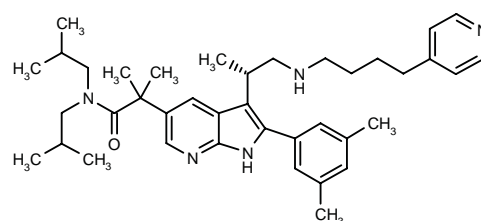
SOURCE – Merck & Co.

REFERENCES

- Walsh, T.F. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9951232.

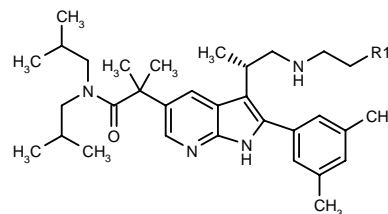
281725

2-[2-(3,5-Dimethylphenyl)-3-[1(S)-methyl-2-[4-(4-pyridinyl)butylamino]ethyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-N,N-diisobutyl-2-methylpropionamide



C39 H55 N5 O; Mol wt: 609.8975

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	R1	Formula
281726	4-Pyr	C ₃₇ H ₅₁ N ₅ O
281727	2-Me-1-oxido-4-Pyr	C ₃₈ H ₅₃ N ₅ O ₂
281728	2-Me-1-oxido-4-Pyr-CH2	C ₃₉ H ₅₅ N ₅ O ₂
281729	5-benzotriazolyl	C ₃₈ H ₅₁ N ₇ O
281730	5-benzotriazolyl-CH2	C ₃₉ H ₅₃ N ₇ O
281731	1-Me-6-oxo-1,6-dihydro-3-Pyr	C ₃₈ H ₅₃ N ₅ O ₂
281811	4-Pyr-CH2	C ₃₈ H ₅₃ N ₅ O

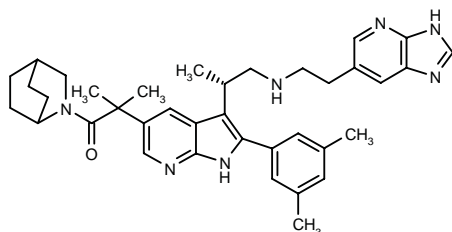
SOURCE – Merck & Co.

REFERENCES

- Walsh, T.F. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9951233.

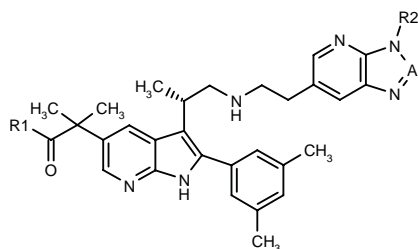
281732

1-(2-Azabicyclo[2.2.2]oct-2-yl)-2-[2-(3,5-dimethylphenyl)-3-[2-[2-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethylamino]-1(*S*)-methylethyl]-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2-methylpropan-1-one



C37 H45 N7 O; Mol wt: 603.8105

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
281733	2-azabicyclo[2.2.2]oct-2-yl	Me	CH	C ₃₈ H ₄₇ N ₇ O
281735	2-azabicyclo[2.2.2]oct-2-yl	H	N	C ₃₆ H ₄₄ N ₈ O
281737	7-azabicyclo[2.2.1]hept-7-yl	Me	CH	C ₃₇ H ₄₅ N ₇ O
281739	7-azabicyclo[2.2.1]hept-7-yl	H	N	C ₃₅ H ₄₂ N ₈ O
281814	7-azabicyclo[2.2.1]hept-7-yl	H	CH	C ₃₆ H ₄₃ N ₇ O

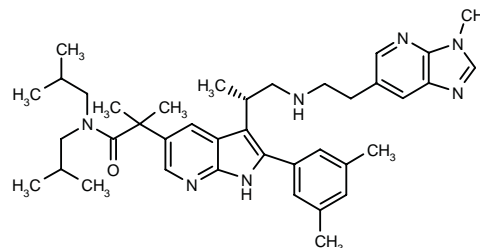
SOURCE – Merck & Co.

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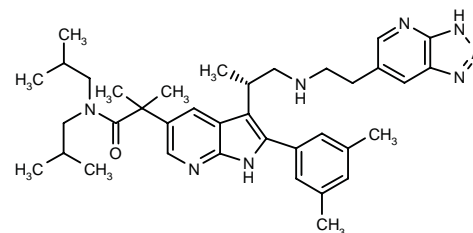
281740

2-[2-(3,5-Dimethylphenyl)-3-[1(*S*)-methyl-2-[2-(3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethylamino]ethyl]-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-*N,N*-diisobutyl-2-methylpropionamide



C39 H53 N7 O; Mol wt: 635.8957

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	A	Formula
281742	N	C ₃₇ H ₅₀ N ₈ O
281815	CH	C ₃₈ H ₅₁ N ₇ O

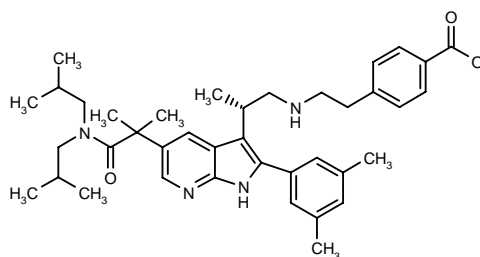
SOURCE – Merck & Co.

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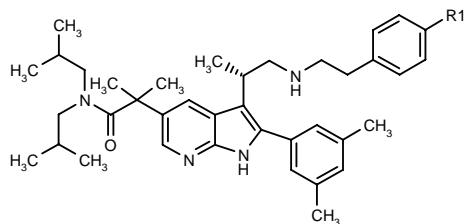
281768

4-[2-[2(*S*)-[5-[1-(*N,N*-Diisobutylcarbamoyl)-1-methylethyl]-2-(3,5-dimethylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propylamino]ethyl]benzoic acid



C39 H52 N4 O3; Mol wt: 624.8648

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	R1	Formula
281769	CO2Me	C ₄₀ H ₅₄ N ₄ O ₃
281826	NHSO2Me	C ₃₉ H ₅₃ N ₅ O ₃ S

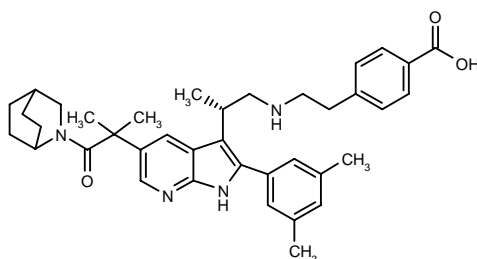
SOURCE – Merck & Co.

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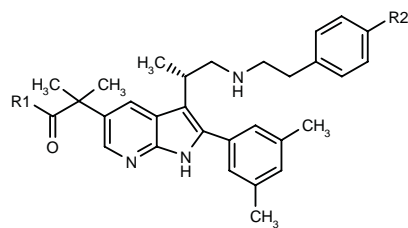
281791

4-[2-[2(*S*)-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]propylamino]ethyl]benzoic acid



C38 H46 N4 O3; Mol wt: 606.8064

ACTION – Nonpeptide gonadotropin-releasing hormone (GnRH) antagonist expected to be useful in the treatment of a variety of sex hormone-related conditions in men and women including endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasias such as prostate, breast and ovarian cancer, sleep apnea, irritable bowel syndrome, premenstrual syndrome and benign prostatic hypertrophy. It may also be beneficial as an adjunct in the treatment of growth hormone deficiency and short stature, for the treatment of systemic lupus erythematosus, in *in vitro* fertilization and as a contraceptive. Other specifically claimed compounds are:



Compound	R1	R2	Formula
281792	2-azabicyclo[2.2.2]oct-2-yl	CO2Et	C ₄₀ H ₅₀ N ₄ O ₃
281793	7-azabicyclo[2.2.1]hept-7-yl	NHSO2Me	C ₃₇ H ₄₇ N ₅ O ₃ S
281794	7-azabicyclo[2.2.1]hept-7-yl	CO2H	C ₃₇ H ₄₄ N ₄ O ₃
281795	7-azabicyclo[2.2.1]hept-7-yl	CO2Et	C ₃₉ H ₄₆ N ₄ O ₃
281834	2-azabicyclo[2.2.2]oct-2-yl	NHSO2Me	C ₃₈ H ₄₈ N ₅ O ₃ S

SOURCE – Merck & Co.

REFERENCES

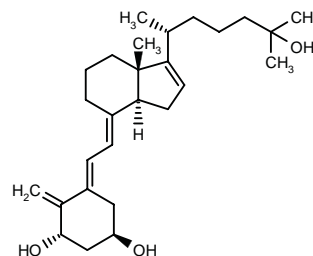
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RO-25-4020

280552

9,10-Secocholesta-5(*E*),7(*E*),10(19),16-tetraene-1 α ,3 β ,25-triol

(5,6-*trans*)-1 α ,25-Dihydroxy-16,17-didehydrovitamin D₃



C27 H42 O3; Mol wt: 414.6258

ACTION – Antineoplastic agent, an analogue of vitamin D₃ with 10-100-fold greater antiproliferative activity than 1,25-dihydroxyvitamin D₃ against human myeloid leukemia HL-60, breast carcinoma MCF-7 and prostate carcinoma LNCaP cell lines (ED₅₀ = 0.03, 4.3 and 1.4 nM, respectively, vs. 4.0, 73 and 23 nM, respectively, for 1,25-dihydroxyvitamin D₃). Compound caused cell cycle arrest in the G0-G1 phase, associated with an elevation in the expression of the cyclin-dependent kinase (CDK) inhibitors p21^{waf1} and p27^{kip1}. In addition, it almost completely inhibited telomerase activity, as well as human telomerase reverse transcriptase. In contrast to 1,25-dihydroxyvitamin D₃, it had very weak calcemic effects, causing no calcemia in mice after 5 weeks of 4 μ g i.p. 3 times/week. Selected for further testing in *in vivo* cancer models.

SOURCE – Roche.

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CANCER IMMUNOTHERAPY

MAb G250

211562

IgG₁ murine monoclonal antibody specific for renal cell carcinoma antigen G250

G250

ACTION – Monoclonal antibody to G250 antigen expressed in renal carcinoma cells. Phase I clinical trials demonstrated excellent localization of murine antibody in renal tumors; phase II clinical trials indicated that radiolabeled antibody was able to deliver tumor-sterilizing radiation doses directly to the tumor, but also that it induced reversible liver function abnormalities and that the maximum tolerated dose of 90 mCi/m² [¹³¹I] induced severe thrombocytopenia in 2 of the first 6 patients. Although 17 of 33 patients had stable disease and 2 had tumor shrinkage, immunogenicity restricted therapy to a single infusion. A chimeric antibody has now been constructed and results from a presurgical trial demonstrated excellent targeting to renal cell carcinoma with no evidence of immune responses; radioimmunotherapy trials of both single and multiple doses in patients with metastatic RCC are currently in progress.

SOURCES – Centocor; Wilex.

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15. Peter, M. et al. *G250, a tumor antigen with therapeutic potential in renal cell carcinoma (RCC)*. 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 652.

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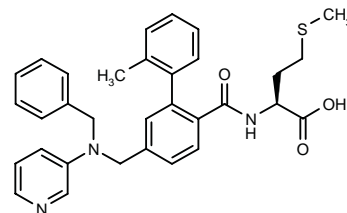
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26. Centocor, Inc. Annual Report 1994.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

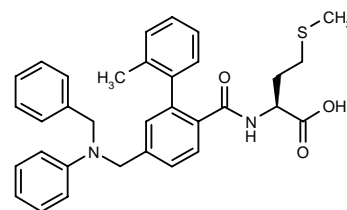
280310

N-[5-[*N*-Benzyl-*N*-(3-pyridyl)aminomethyl]-2'-methylbiphenyl-2-ylcarbonyl]-L-methionine



C32 H33 N3 O3 S; Mol wt: 539.6967

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC₅₀ = 0.1 nM) and of Ras farnesylation in whole cells (ED₅₀ = 0.013 nM in NIH3T3 cells). Despite its poor pharmacokinetic profile following i.v. or i.d. dosing in rats (i.v. t_{1/2} = 0.83 h, i.d. AUC < 1 µg.h/ml), compound (25 mg/kg/day i.p.) showed good antitumor efficacy against human pancreatic MiaPaCa tumors containing a K-ras mutation or human lung adenocarcinoma A-549 inoculated s.c. to nude mice. Another related compound is:



280311: C33 H34 N2 O3 S

SOURCES – Abbott; University of Pittsburgh, Pittsburgh, PA (US).

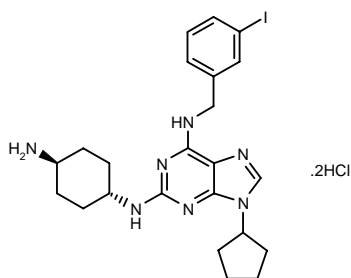
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280370

trans-*N*²-(4-Aminocyclohexyl)-9-cyclopentyl-*N*⁶-(3-iodobenzyl)-9*H*-purine-2,6-diamine dihydrochloride



C23 H30 I N7 . 2HCl; Mol wt: 604.3608

ACTION – Agent for the treatment of proliferative disorders and neurodegenerative diseases, a selective cyclin-dependent kinase CDK2 inhibitor (IC_{50} = 0.037-0.085 μ M vs. IC_{50} = 2.0 μ M against CDK4) with *in vitro* antiproliferative activity against a panel of human cell cancer lines including breast adenocarcinoma MCF-7 and MDA-MB-231 (IC_{50} = 0.6 and 0.8 μ M, respectively), lung carcinoma A549 and DMS114 (IC_{50} = 1.0 and 0.9 μ M, respectively), colon carcinoma HT-29 and HCT15 (IC_{50} = 0.9 and 1.9 μ M, respectively), and prostate carcinoma PC-3 and DU145 (IC_{50} = 1.1 and 1.2 μ M, respectively). *In vivo*, it was shown to inhibit the growth of PC-3 prostate tumors in a subrenal capsule assay in nude mice (T/C x 100 = 44% at 3 mg/kg/day i.p. x 12 days). A representative compound from a series of 6,9-disubstituted 2-[*trans*-(4-aminocyclohexyl)amino]purines.

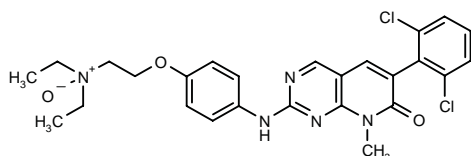
SOURCE – Hoechst Marion Roussel (Aventis).

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280383

6-(2,6-Dichlorophenyl)-2-[4-[2-(*N,N*-diethyl-*N*-oxido-amino)ethoxy]phenylamino]-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one



C26 H27 Cl2 N5 O3; Mol wt: 528.4373

ACTION – Agent for the treatment of cancer, atherosclerosis, restenosis and psoriasis that acts by inhibiting protein tyrosine kinases such as platelet-derived growth factor (PDGF) receptor, fibroblast growth factor (FGF) receptor and C-src tyrosine kinases (IC_{50} = 0.07, 0.063 and 0.015 μ M, respectively), reported to be a metabolite of the known kinase inhibitor PD-166285*.

SOURCE – Warner-Lambert.

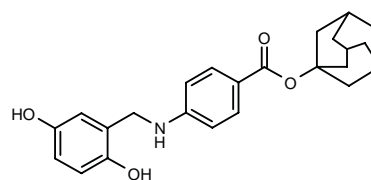
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*See **PD-164771** Drug Data Rep 1996, 018(11): 0977.

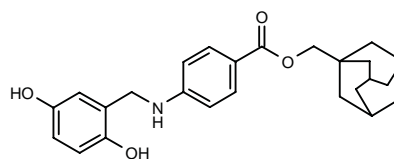
280448

4-(2,5-Dihydroxybenzylamino)benzoic acid 1-adamantyl ester



C24 H27 N O4; Mol wt: 393.4803

ACTION – Antiproliferative agent with protein tyrosine kinase-inhibitory activity, giving an IC_{50} value of 13.60 ± 1.81 μ M for inhibition of p210^{bcr-abl} autophosphorylation. Antitumor activity was demonstrated *in vitro* in the NCI panel of 60 tumor cell lines (mean $\log GI_{50}$ = -6.03) and *in vivo* in mice bearing s.c. tumor xenografts. Another specifically claimed compound from this series of disubstituted lavendustin A analogues is:



280449: C25 H29 N O4

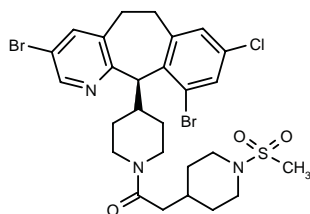
SOURCE – Department of Health & Human Services (US).

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1. Narayanan, V.L. et al. (Department of Health & Human Services) *Disubst. lavendustin A analogs and pharmaceutical compsns. comprising the analogs*. WO 9943636.

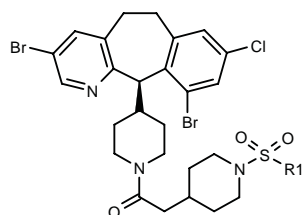
280681

1-[4-[8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-2-[1-(methylsulfonyl)piperidin-4-yl]ethan-1-one



C₂₇ H₃₂ Br₂ Cl N₃ O₃ S; Mol wt: 673.8948

ACTION – Antineoplastic agent, a potent and selective inhibitor of protein farnesyltransferase (IC₅₀ = 2.1 nM) proven to inhibit Ras processing in COS cells (IC₅₀ = 30 nM). Other related tricyclic compounds include the following:



Compound	R1	Formula
280682	Et	C ₂₈ H ₃₄ Br ₂ ClN ₃ O ₃ S
280683	Pr	C ₂₉ H ₃₆ Br ₂ ClN ₃ O ₃ S
280684	N(Me) ₂	C ₂₈ H ₃₅ Br ₂ ClN ₄ O ₃ S

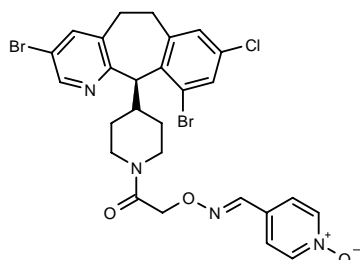
SOURCE – Schering-Plough.

REFERENCES

1. Taveras, A.G. et al. (Schering Corp.) *Cpds. useful for inhibition of farnesyl protein transferase*. US 5945429.

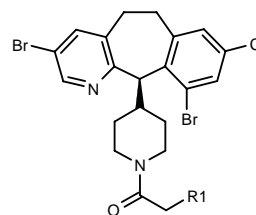
280707

(+)-1-Oxidopyridine-4-carbaldehyde O-[2-[4-[3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]-1-piperidinyl]-2-oxoethyl]oxime



C₂₇ H₂₅ Br₂ Cl N₄ O₃; Mol wt: 648.7805

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC₅₀ = 0.0036 μM) and of the farnesylation of the oncogene protein Ras. Within this series of aminoxyamide tricyclic compounds, the following are also included:



Compound	R1	Formula
280708	ONHCOPh	C ₂₈ H ₂₆ Br ₂ ClN ₃ O ₃
280709	ON=C(Me) ₂	C ₂₄ H ₂₆ Br ₂ ClN ₃ O ₂
280710	CH ₂ ON=C(Me) ₂	C ₂₅ H ₂₈ Br ₂ ClN ₃ O ₂
280711	cyclohexyl=NO	C ₂₇ H ₃₀ Br ₂ ClN ₃ O ₂
280712	1,4-dioxaspiro[4.5]decan-8-yl=NO	C ₂₉ H ₃₂ Br ₂ ClN ₃ O ₄
280713	tetrahydropyran-4-yl=NO	C ₂₆ H ₂₈ Br ₂ ClN ₃ O ₃
280714	tetrahydrothiopyran-4-yl=NO	C ₂₆ H ₂₈ Br ₂ ClN ₃ O ₂ S
280715	ONHAc	C ₂₃ H ₂₄ Br ₂ ClN ₃ O ₃
280716	NH ₂ O	C ₂₆ H ₃₀ Br ₂ ClN ₃ O ₄

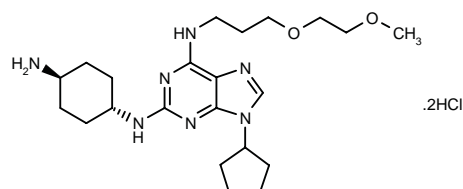
SOURCE – Schering-Plough.

REFERENCES

1. Doll, R.J. and Lalwani, T. (Schering Corp.) *Aminoxyamide tricyclic inhibitors of farnesyl-protein transferase*. US 5945430.

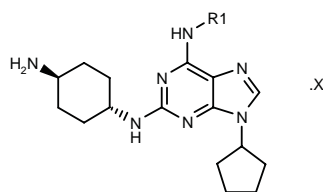
280869

trans-*N*²-(4-Aminocyclohexyl)-9-cyclopentyl-*N*⁶-[3-(2-methoxyethoxy)propyl]-9*H*-purine-2,6-diamine dihydrochloride



C₂₂ H₃₇ N₇ O₂ . 2HCl; Mol wt: 504.5031

ACTION – Antineoplastic agent, a selective cyclin-dependent kinase CDK2 and CDK4 inhibitor (IC₅₀ = 0.016 and 0.04 μM, respectively) with *in vitro* antiproliferative activity against a panel of human cancer cell lines including breast adenocarcinoma MDA-MB-231 (IC₅₀ = 1.8 μM), lung carcinoma A549 and DMS114 (IC₅₀ = 1.2 and 1.8 μM, respectively), colon carcinoma HT-29 and Colo-205 (IC₅₀ = 2.1 and 1.6 μM, respectively) and prostate carcinoma PC-3 and DU145 (IC₅₀ = 1.4 and 1.8 μM, respectively). Other exemplified compounds from this series of 6,9-disubstituted 2-[*trans*-(4-aminocyclohexyl)-amino]purines include the following:



Compound	R1	X	Formula
280870	CH ₂ CH ₂ NHPh	3HCl	C ₂₄ H ₃₄ N ₈ ·3HCl
280871	Ph	2HCl	C ₂₂ H ₂₉ N ₇ ·2HCl
280872	1-(4-MeO-PhCH ₂)-4-Pip		C ₂₉ H ₄₂ N ₈ O
280873	1-(3-Cl-PhCH ₂)-4-Pip		C ₂₈ H ₃₉ ClN ₈
280875	1-[3,5-(MeO)2-PhCH ₂]-4-Pip	3HCl	C ₃₀ H ₄₄ N ₈ O ₂ ·3HCl
280876	1-(3-Me-PhCH ₂)-4-Pip	3HCl	C ₂₉ H ₄₂ N ₈ ·3HCl
280877	1-(2-MeO-PhCH ₂)-4-Pip	3HCl	C ₂₉ H ₄₂ N ₈ O·3HCl

Compounds of the invention are also reported to be effective in preventing apoptosis in neuronal cells induced by antineoplastic agents or resulting from cerebrovascular disease, oxygen depletion, stroke or infarction.

SOURCE – Hoechst Marion Roussel (Aventis).

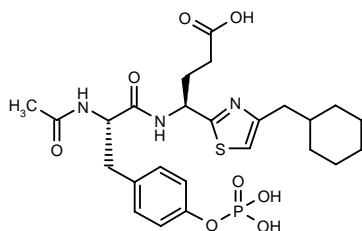
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- Dumont, J.A. et al. (Hoechst Marion Roussel, Inc.) *6,9-Disubst. 2-[trans(4-aminocyclohexyl)amino]purines*. WO 9943675.

281268

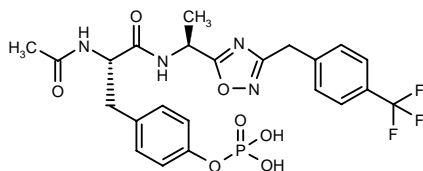
4(S)-[2(S)-Acetamido-3-[4-(phosphonoxy)phenyl]-propionamido]-4-[4-(cyclohexylmethyl)thiazol-2-yl]butyric acid

*N*²-Acetyl-*N*¹-[3-carboxy-1-[4-(cyclohexylmethyl)thiazol-2-yl]propyl]-4-*O*-(phosphono)-L-tyrosinamide



C₂₅ H₃₄ N₃ O₈ P S; Mol wt: 567.5966

ACTION – Agent for the treatment of cancer, restenosis, osteoporosis, inflammation, allergy and cardiovascular disorders that acts by inhibiting SH₂-mediated signal transduction. Another exemplified compound from this broad class of heterocyclic signal transduction inhibitors is:



281271: C₂₃ H₂₄ F₃ N₄ O₇ P

SOURCE – Ariad.

REFERENCES

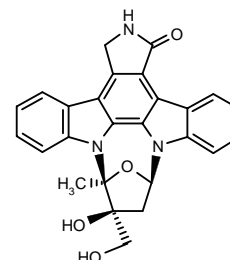
- Buchanan, J. et al. (Ariad Pharmaceuticals Inc.) *Heterocyclic signal transduction inhibitors, compsns. containing them*. WO 9947529.

CEP-701*

146816

9(*S*),12(*R*)-Epoxy-10(*S*)-hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydroindolo[1,2,3-fg:3',2',1'-k]-pyrrolo[3,4-*l*][1,6]benzodiazocin-1-one

KT-5555



C₂₆ H₂₁ N₃ O₄; Mol wt: 439.4689

ACTION – Antineoplastic agent, a Trk tyrosine kinase inhibitor (IC₅₀ = 3.7 nM against TrkA) that also inhibits vascular endothelial growth factor (VEGF) receptor kinase VEGF-R2/flk-1 (IC₅₀ = 65 nM) and platelet-derived growth factor (PDGF) receptor β kinase (IC₅₀ = 216 nM). Compound was able to induce apoptosis in prostate cancer cells by inhibiting Trk kinase activity and by delaying elevation of intracellular free Ca²⁺. In s.c. xenograft models of human pancreatic ductal adenocarcinoma (PDAC) including Panc-1, AsPc-1, BXPc-3, Colo357 and MiaPaCa2 xenografts, compound given at 10 mg/kg s.c. b.i.d. for 21-28 days significantly inhibited tumor growth. It also inhibited *in vivo* tumor invasiveness in four rat tracheal xenografts. The *in vivo* antitumor effects were observed in the absence of morbidity or toxicity. Currently in clinical trials as an oral agent for the treatment of PDAC.

SOURCES – Cephalon; Kyowa Hakko; Schwarz; TAP.

REFERENCES

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- Hirata, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *K-252 derivs*. JP 87155285.
- Lewis, M.E. et al. (Cephalon, Inc.;Kyowa Hakko Kogyo Co., Ltd.) *Bis-staurosporine and K-252a derivs*. EP 651754, EP 768312, JP 96501081, US 5461146, WO 9402488.
- Lewis, M.E. et al. (Cephalon, Inc.;Kyowa Hakko Kogyo Co., Ltd.) *Protein kinase inhibitors for treatment of neurological disorders*. EP 788501, JP 98510514, WO 9613506, WO 9613506.
- Murakata, C. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Derivs. of physiologically active substance K-252*. EP 303697, WO 8807045.
- George, D.J. et al. *Sustained in vivo regression of Dunning H rat prostate cancers treated with combinations of androgen ablation and Trk tyrosine kinase inhibitors, CEP-751 (KT-6587) or CEP-701 (KT-5555)*. Cancer Res 1999, 59(10): 2395.
- Miknyoczki, S.J. et al. *The novel Trk receptor tyrosine kinase inhibitor CEP-701 (KT-5555) exhibits antitumor efficacy against human pancreatic carcinoma (Panc1) xenograft growth and in vivo invasiveness*. Ann New York Acad Sci 1999, 880: 252.
- Miknyoczki, S.J. et al. *The Trk tyrosine kinase inhibitor CEP-701 (KT-5555) exhibits significant anti-tumor efficacy in pre-clinical xenograft models of human pancreatic ductal carcinoma*. Proc Amer Assoc Cancer Res 1999, 40: Abst 3199.
- Miknyoczki, S.J. et al. *The Trk tyrosine kinase inhibitor CEP-701 (KT-5555) exhibits significant antitumor efficacy in preclinical xenograft models of human pancreatic ductal adenocarcinoma*. Clin Cancer Res 1999, 5(8): 2205.

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12. Weeratna, A.T. et al. *The tyrosine kinase inhibitors CEP-751 (KT-6587) and CEP-701 (KT-5555) lead to apoptosis in prostate cancer cells via the elevation of intracellular free calcium and inhibition of the PI-3 kinase/PKB pathway.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abstr 104.

13. *Cephalon presents CEP-701 at German cancer meeting.* DailyDrugNews.com (Daily Essentials) 1998, Sept 22.

14. *Cephalon provides investor update on product development programs.* DailyDrugNews.com (Daily Essentials) 1998, Aug 13.

15. *Cephalon provides update on product development programs.* DailyDrugNews.com (Daily Essentials) 1999, Dec 30.

*Identified compound **146816** (see **141874**) Drug Data Rep 1989, 011(01): 0071.

HPKCI

280441

Human protein kinase C inhibitor

ACTION – Novel human protein kinase C (PKC) inhibitor polypeptide identified from an ileal tissue cDNA library with potential in the diagnosis, treatment and/or prevention of cancer, autoimmune diseases and cognitive disorders. Polynucleotides encoding the new inhibitor and compositions thereof, as well as antibodies to and agonists and antagonists of the polypeptide are also provided.

SOURCE – Incyte.

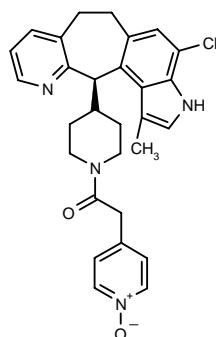
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SCH-207758

279790

4-Chloro-1-methyl-12(*R*)-[1-[2-(1-oxidopyridin-4-yl)-2-oxoethyl]piperidin-4-yl]-3,6,7,12-tetrahydropyrido[3',2':5,6]-cyclohepta[1,2-*e*]indole



C29 H29 Cl N4 O2; Mol wt: 501.0271

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase ($IC_{50} = 7.5$ nM) with good oral bioavailability and sustained plasma levels and exposure following i.v. administration in mice.

SOURCE – Schering-Plough.

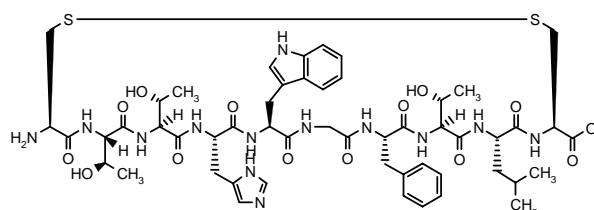
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1. Vaccaro, C.J. et al. *Discovery of indolocycloheptapyridine inhibitors of farnesyl protein transferase by de novo analysis of the X-ray crystal structure of Sch-66336-r-FPT.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abstr 165.

ANGIOGENESIS INHIBITORS

279831

L-Cysteinyl-L-threonyl-L-threonyl-L-histidyl-L-tryptophyl-glycyl-L-phenylalanyl-L-threonyl-L-leucyl-L-cysteine cyclic (1-10)-disulfide



C52 H71 N13 O14 S2; Mol wt: 1166.3420

ACTION – Tumor-targeting antiangiogenic and anti-invasive agent, a synthetic cyclic peptide that acts as a selective inhibitor of gelatinase with preferential activity against gelatinase A (MMP-2; $IC_{50} = 10$ μ M) compared to gelatinase B (MMP-9; $IC_{50} > 10$ μ M) and selectivity over other matrix metalloproteinases (MMPs). Compound was able to inhibit the migration of various cell lines *in vitro*, including fibrosarcoma HT1080, melanoma C8161, ovarian carcinoma SKOV-3 and Kaposi's sarcoma KS1767 cell lines, without inducing cytotoxicity. It was also able to prevent tumor growth and invasion in animal models and improved survival in mice bearing human tumor xenografts. A compound-displaying phage was found to specifically target angiogenic blood vessels in mice following i.v. injection.

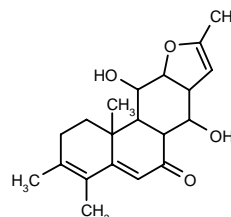
SOURCES – Burnham Institute, La Jolla, CA (US); University of Helsinki, Helsinki (FI).

REFERENCES

1. Koivunen, E. et al. *Tumor targeting with a selective gelatinase inhibitor.* Nat Biotechnol 1999, 17(8): 768.

280943

7,11-Dihydroxy-3,4,9,11b-tetramethyl-1,2,6,6a,7,7a,10a,11,11a,11b-decahydrophenanthro[3,2-*b*]furan-6-one



C20 H26 O4; Mol wt: 330.4214

ACTION – Antiangiogenic agent isolated from the plant *Ajuga reptans*, proven active in a collagen tube formation assay. Potentially useful for the treatment of angiogenic conditions such as diabetic retinopathy, cancer, arthritis, psoriasis and hemangioma.

SOURCE – Phytera.

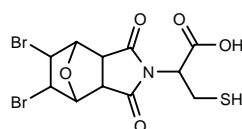
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1. Gulavita, N.K. et al. (Phytera, Inc.) *Phenanthrofuran derivs.* US 5981574, WO 9945919.

OTHER ONCOLYTIC DRUGS

279681

2-(8,9-Dibromo-3,5-dioxo-10-oxa-4-azatricyclo-[5.2.1.0^{2,6}]dec-4-yl)-3-sulfanylpropionic acid



C11 H11 Br2 N O5 S; Mol wt: 429.0839

ACTION – Antineoplastic agent, a 5,6-dibromo norcantharidinimide derivative showing high uptake into the liver, lungs and kidneys when labeled with [¹²⁵I].

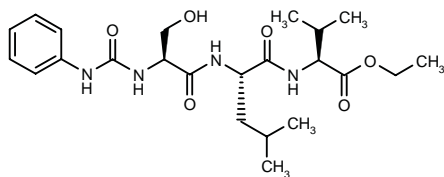
SOURCE – Beijing Normal University, Beijing (CN).

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1. Li, T.H. et al. *Synthesis of 5,6-dibromocantharidinimide derivatives, iodine-125 labelling and in animal distribution.* Chin J Med Chem 1999, 9(1): 46.

279997

N-(*N*-Phenylcarbamoyl)-L-seryl-L-leucyl-L-valine ethyl ester



C23 H36 N4 O6; Mol wt: 464.5594

ACTION – Antineoplastic agent, a tripeptide ester derivative of Fas that was shown to induce apoptosis in human colon cancer DLD-1 cells, which was dependent on anti-Fas antibody levels.

SOURCE – Kirin Brewery.

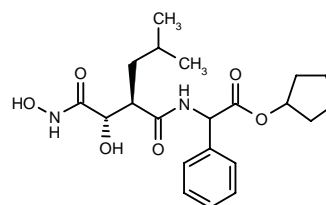
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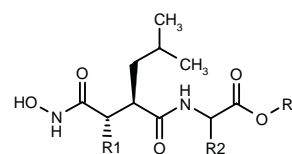
281076

2-[2(*R*)-[1(*S*)-Hydroxy-1-(*N*-hydroxycarbamoyl)methyl]-4-methylpentanamido]-2-phenylacetic acid cyclopentyl ester



C21 H30 N2 O6; Mol wt: 406.4760

ACTION – Antineoplastic agent particularly useful for inhibiting the proliferation of rapidly dividing tumor cells such as melanoma and lymphoma cells, a representative compound from a series of specifically claimed hydroxy-carbamoyl derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
281078	OMe	Ph	cyclopentyl	C ₂₂ H ₃₂ N ₂ O ₆
281080	allyl	4-MeO-Ph	cyclopentyl	C ₂₅ H ₃₆ N ₂ O ₆
281084	allyl	2-thienyl	cyclopentyl	C ₂₂ H ₃₂ N ₂ O ₅ S
281085	allyl	3-thienyl	cyclopentyl	C ₂₂ H ₃₂ N ₂ O ₅ S
281087	allyl	Ph	i-Pr	C ₂₂ H ₃₂ N ₂ O ₅

SOURCE – British Biotech.

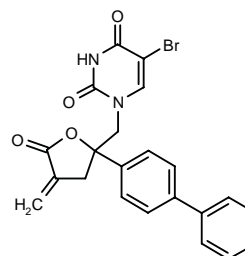
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281302

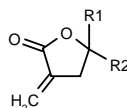
1-[2-(Biphenyl-4-yl)-4-methylene-5-oxotetrahydrofuran-2-ylmethyl]-5-bromo-1,2,3,4-tetrahydropyrimidine-2,4-dione

1-[2-(Biphenyl-4-yl)-4-methylene-5-oxotetrahydrofuran-2-ylmethyl]-5-bromouracil



C22 H17 Br N2 O4; Mol wt: 453.2903

ACTION – Antineoplastic agent, a representative compound from a series of α-methylene-γ-butyrolactones, wherein the following are also included:



Compound	R1	R2	Formula
281303	4-Ph-Ph	thymine-1-yl-CH ₂	C ₂₃ H ₂₀ N ₂ O ₄
281304	4-Cl-Ph	thymine-1-yl-CH ₂	C ₁₇ H ₁₅ ClN ₂ O ₄
281305	Ph	2-oxo-2H-1-benzopyran-4-yl-OCH ₂	C ₂₁ H ₁₆ O ₅
281306	Me	2-oxo-2H-1-benzopyran-7-yl-OCH ₂	C ₁₈ H ₁₄ O ₅
281307	Ph	3-Cl-4-Me-2-oxo-2H-1-benzopyran-7-yl-OCH ₂	C ₂₂ H ₁₇ ClO ₅
281308	H	4-[1,3-dioxo-2-isindolyl-(CH ₂) ₃ O]-Ph	C ₂₂ H ₁₉ N ₂ O ₅

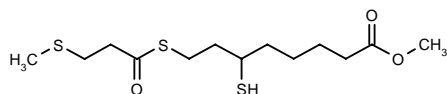
SOURCE – National Science Council, Taiwan, Taipei (TW).

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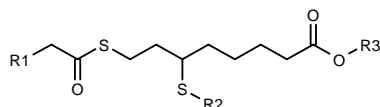
281454

8-[3-(Methylsulfanyl)propionylsulfanyl]-6-sulfanyloctanoic acid methyl ester



C₁₃ H₂₄ O₃ S₃; Mol wt: 324.5276

ACTION – Antineoplastic agent that acts by selectively inducing apoptosis of tumor or transformed cells. *In vitro*, compound produced 40 and 70% inhibition of the proliferation of HeLa cells at 400 and 600 μM, respectively, while it produced only 5-10% inhibition of the growth of normal fibroblast MRC-5 cells at the same concentrations. In addition, it was shown to induce an increase in DNA fragmentation in HeLa cells of about 17 and 30% at 100 and 200 μM, respectively. Antitumor activity was also demonstrated *in vivo* in mice with s.c.-implanted murine melanoma B16, where only 10 and 20% of mice receiving 50 and 100 mg/kg/day i.p. x 15 days, respectively, developed tumors compared to 50% of animals in the control group. Other compounds from this series of substituted 6,8-dimercaptooctanoic acid derivatives include the following:



Compound	R1	R2	R3	Formula
281455	CH ₂ SM _e	COCH ₂ CH ₂ SM _e	Me	C ₁₇ H ₃₀ O ₄ S ₄
281456	CH ₂ SM _e	H	t-Bu	C ₁₆ H ₃₀ O ₃ S ₃
281457	CH ₂ SM _e	COCH ₂ CH ₂ SM _e	t-Bu	C ₂₀ H ₃₆ O ₄ S ₄
281458	CH ₂ SM _e	COCH ₂ CH ₂ SM _e	Bu	C ₂₀ H ₃₆ O ₄ S ₄
281459	CH ₂ SM _e	COCH ₂ CH ₂ SM _e	CH ₂ CH ₂ -N ⁺ (Me) ₃ I ⁻	C ₂₁ H ₄₀ INO ₄ S ₄
281460	H	COCH ₂ CH ₂ SM _e	Me	C ₁₅ H ₂₆ O ₄ S ₃

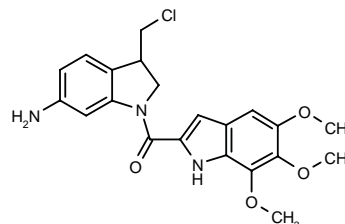
SOURCE – Galderma.

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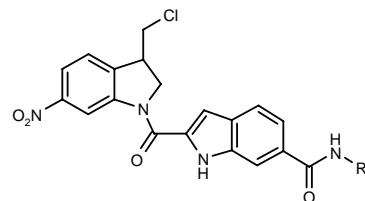
282940

1-[6-Amino-3-(chloromethyl)-2,3-dihydro-1H-indol-1-yl]-1-(5,6,7-trimethoxy-1H-indol-2-yl)methanone



C₂₁ H₂₂ Cl N₃ O₄; Mol wt: 415.8748

ACTION – Anticancer agent that may be used to selectively kill oxidic and hypoxic tumor cells for the treatment of leukemia and, particularly, solid tumors including breast, colon and lung tumors. It can also be used in conjunction with nitroreductase or carboxypeptidase enzymes in antibody-directed enzyme/prodrug therapy (ADEPT) or gene-directed enzyme/prodrug therapy (GDEPT). Significant activation of the compound by *Escherichia coli* nitroreductase enzyme was observed in UV4 cells under aerobic conditions. Other specifically claimed compounds are:



Compound	R1	Formula
282943	2-Pyr-CH ₂ CH ₂	C ₂₆ H ₂₂ ClN ₃ O ₄
282944	4-morpholinyl-CH ₂ CH ₂	C ₂₅ H ₂₆ ClN ₃ O ₅
282945	CH(CH ₂ OH) ₂	C ₂₂ H ₂₁ ClN ₃ O ₆
282946	CH ₂ CO ₂ H	C ₂₁ H ₁₇ ClN ₃ O ₆

SOURCE – Cancer Research Campaign Technology.

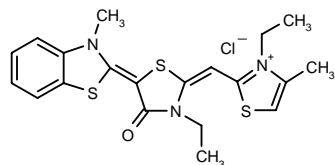
REFERENCES

1. Denny, W.A. and Tercel, M. (Cancer Research Campaign Technology Ltd.) *Cyclopropylindoles and their seco precursors, and their use as prodrugs*. US 5985909, WO 9707097.

FJ-5002

280556

3-Ethyl-2-[3-ethyl-5-(3-methyl-2,3-dihydrobenzothiazol-2-ylidene)-4-oxo-2,3,4,5-tetrahydrothiazol-2-ylidenemethyl]-4-methyl-3-thiazolium chloride



C20 H22 Cl N3 O S3; Mol wt: 452.0648

ACTION – Antineoplastic agent, a potent and competitive telomerase inhibitor ($K_i \sim 1.8 \mu\text{M}$) found to be effective in inducing telomerase erosion, increase in chromosome abnormalities, senescence/crisis-like features and loss of cellular viability in human leukemia U937 cells. The acetate form showed selective *in vitro* cytotoxic activity against human colon carcinoma CX-1 and human epidermoid carcinoma KB cells ($\text{IC}_{50} = 0.11$ and $0.95 \mu\text{M}$, respectively) over normal kidney CV-1 cells ($\text{IC}_{50} = 23.6 \mu\text{M}$). *In vivo*, the acetate form (4 mg/kg/day i.p. for 5 days) exhibited marked efficacy against human melanoma LOX xenografts in nude mice, as well as against adenocarcinoma CA755 allografts in BDF1 mice (3 mg/kg/day i.v. for 4 days); the LD_{50} values in mice were 20 mg/kg i.v. and > 30 mg/kg i.p.

SOURCES – Dana-Farber Cancer Institute, Boston, MA (US); Fuji Photo Film.

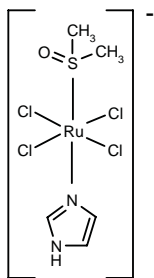
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4. Naasani, I. et al. *FJ5002: A potent telomerase inhibitor identified by exploiting the disease-oriented screening program with COMPARE analysis*. Cancer Res 1999, 59(16): 4004.

NAMI-A

278746

1*H*-Imidazolium (OC-6-11)-tetrachloro(1*H*-imidazole- κN^3)-[(sulfanyl- κS)bis[methane]]ruthenate(1-)



C3 H5 N2 . C3 H4 N2 . C2 H6 O S . Cl4 Ru; Mol wt: 458.1815

ACTION – Antimetastatic agent, a ruthenium complex active against lung metastases from solid tumors. *In vitro*, in contrast to cisplatin, compound was devoid of cytotoxicity up to $100 \mu\text{M}$ and caused a mild and transient cell cycle arrest in the premitotic G2/M phase. *In vivo* in mouse models of lung metastasis (mammary carcinoma MCa, adenocarcinoma TS/A), compound given i.p. at 35-70 mg/kg/day for 6 days was effective in reducing lung metastasis independent of the tumor line and the stage of metastatic growth; this inhibition was accompanied by a marked deposition of connective tissue fibers around the primary tumor mass and a significant prolongation of survival. It was less toxic than cisplatin in terms of decrease in body weight gain and spleen weight.

SOURCE – Sigea.

REFERENCES

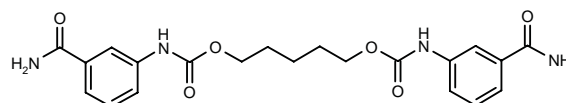
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2. Bergamo, A. et al. *In vitro cell cycle arrest, in vivo action on solid metastasizing tumors, and host toxicity of the antimetastatic drug NAMI-A and cisplatin*. J Pharmacol Exp Ther 1999, 289(1): 559.
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

281313

3,3'-(Pentane-1,5-diyl)bis(oxy)bis(carbonyl)bis(imino)-bis(benzamide)

N-(3-Carbamoylphenyl)carbamic acid diester with pentane-1,5-diol



C21 H24 N4 O6; Mol wt: 428.4426

ACTION – An inhibitor of NAD⁺ ADP-ribosyltransferase, also known as poly(ADP-ribose)polymerase (PARP; IC₅₀ = 0.59 µM against purified rat enzyme), with potential in the treatment or prevention of cancer, stroke, ischemia, restenosis, atherosclerosis and neurodegenerative diseases. A representative compound from a series of bis-benzamide derivatives.

SOURCE – Pierre Fabre.

REFERENCES

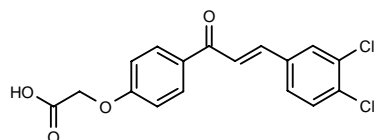
1. Perez, M. et al. (Pierre Fabre Médicament) *Novel bis-benzamide derivs., method for making same, pharmaceutical compns. containing them and use thereof as medicine.* FR 2776291, WO 9947494.

RADIOSENSITIZERS

LSM-83177

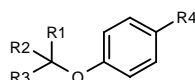
281461

2-[4-[3-(3,4-Dichlorophenyl)-2(*E*)-propenoyl]phenoxy]-acetic acid



C17 H12 Cl2 O4; Mol wt: 351.1838

ACTION – Antineoplastic agent that acts as an antagonist of proto-oncoprotein MDM2 activity, in particular of the interaction of MDM2 with p53, thereby leading to an intracellular increase in active p53, thus allowing p53 protein to promote apoptosis in cancer cells. Compound exhibits low glutathione *S*-transferase-inhibitory activity and was shown to be a potent radiosensitizing agent for doxorubicin-resistant breast cancer MCF-7 cells. Other specifically claimed compounds from this series of phenoxy acetic acid and phenoxymethyl tetrazole derivatives include the following:



Compound	R1=R2	R3	R4	Formula
281462	H	5-tetrazolyl	COCH(Et)-CH ₂ N(Me) ₂	C ₁₅ H ₁₉ Cl ₂ N ₅ O ₂
281463	H	5-tetrazolyl	COC(Et)=CH ₂	C ₁₃ H ₁₂ Cl ₂ N ₄ O ₂
281464	H	2-Me-5-tetrazolyl	COC(Et)=CH ₂	C ₁₄ H ₁₄ Cl ₂ N ₄ O ₂
281465	Me	CO ₂ Et	4-Cl-PhCOCH=CH-CONHCH ₂ CH ₂	C ₂₄ H ₂₄ Cl ₃ N ₅ O ₅

SOURCE – Roche.

REFERENCES

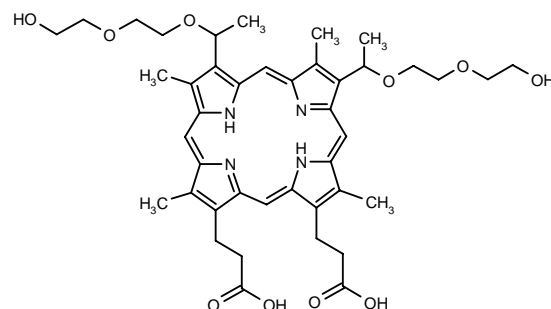
1. Di Dimenico, R. et al. (F. Hoffmann-La Roche AG) *Derivs. of phenoxy acetic acid and phenoxymethyltetrazole having antitumor activity.* CA 2267047, EP 947494, EP 947511.

PHOTOSENSITIZERS

279679

3,8-Bis[1-[2-(2-hydroxyethoxy)ethoxy]ethyl]-2,7,12,18-tetramethylporphyrin-13,17-dipropionic acid

3¹,8¹-Bis[2-(2-hydroxyethoxy)ethoxy]mesoporphyrin



C42 H54 N4 O10; Mol wt: 774.9066

ACTION – Photosensitizer for the photodynamic therapy of tumors, a hematoporphyrin reported to have a stronger photosensitizing effect than porfimer in mice bearing sarcoma 180.

SOURCE – Second Military Medical University, Shanghai (CN).

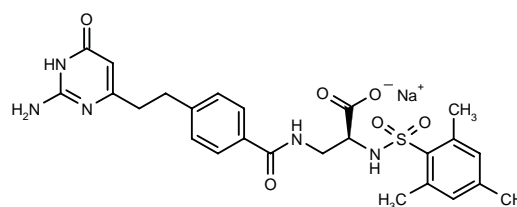
REFERENCES

1. Fan, K.-H. et al. *Hematoporphyrin ethyleneglycolyl ethers: Synthesis and photodynamic effects on tumor.* Zhongguo Yiyao Gongye Zazhi 1999, 30(6): 258.

OCULAR MEDICATIONS

281568

3-[4-[2-(2-Amino-6-oxo-1,6-dihydropyrimidin-4-yl)ethyl]benzamido]-2(*S*)-(2,4,6-trimethylphenyl)sulfonamido]propionic acid sodium salt



C25 H28 N5 Na O6 S; Mol wt: 549.5812

ACTION – An antagonist of integrins such as α_vβ₃ and gpIIb/IIIa with potential in the treatment of angiogenic disorders, inflammation, bone degradation, cancer, diabetic retinopathy, thrombosis, restenosis and macular degeneration. Other specifically claimed compounds include the following:

ACTION – An inhibitor of NAD⁺ ADP-ribosyltransferase, also known as poly(ADP-ribose)polymerase (PARP; IC₅₀ = 0.59 µM against purified rat enzyme), with potential in the treatment or prevention of cancer, stroke, ischemia, restenosis, atherosclerosis and neurodegenerative diseases. A representative compound from a series of bis-benzamide derivatives.

SOURCE – Pierre Fabre.

REFERENCES

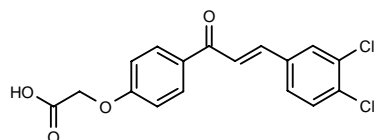
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RADIOSENSITIZERS

LSM-83177

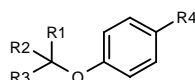
281461

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Compound	R1=R2	R3	R4	Formula
281462	H	5-tetrazolyl	COCH(Et)-CH ₂ N(Me) ₂	C ₁₅ H ₁₉ Cl ₂ N ₅ O ₂
281463	H	5-tetrazolyl	COC(Et)=CH ₂	C ₁₃ H ₁₂ Cl ₂ N ₄ O ₂
281464	H	2-Me-5-tetrazolyl	COC(Et)=CH ₂	C ₁₄ H ₁₄ Cl ₂ N ₄ O ₂
281465	Me	CO ₂ Et	4-Cl-PhCOCH=CH-CONHCH ₂ CH ₂	C ₂₄ H ₂₄ Cl ₃ NO ₅

SOURCE – Roche.

REFERENCES

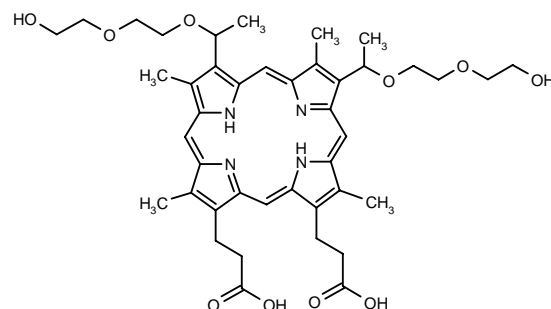
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PHOTOSENSITIZERS

279679

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3¹,8¹-Bis[2-(2-hydroxyethoxy)ethoxy]mesoporphyrin



C42 H54 N4 O10; Mol wt: 774.9066

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SOURCE – Second Military Medical University, Shanghai (CN).

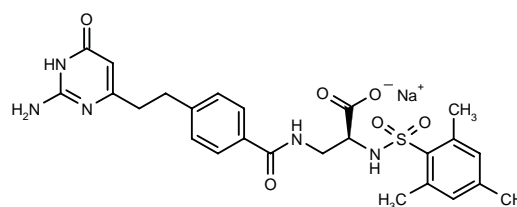
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1. Fan, K.-H. et al. *Hematoporphyrin ethyleneglycolyl ethers: Synthesis and photodynamic effects on tumor.* Zhongguo Yiyao Gongye Zazhi 1999, 30(6): 258.

OCULAR MEDICATIONS

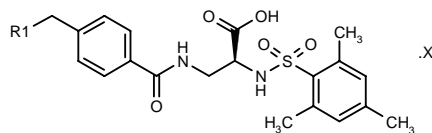
281568

3-[4-[2-(2-Amino-6-oxo-1,6-dihydropyrimidin-4-yl)ethyl]benzamido]-2(*S*)-(2,4,6-trimethylphenyl)sulfonamido]propionic acid sodium salt

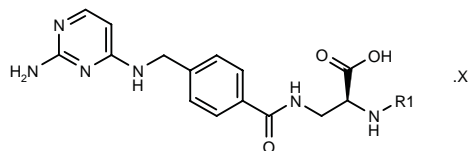


C25 H28 N5 Na O6 S; Mol wt: 549.5812

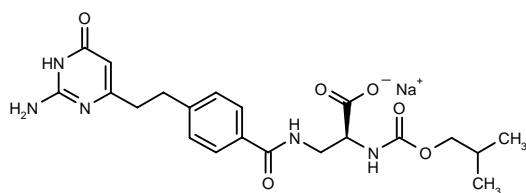
ACTION – An antagonist of integrins such as α_vβ₃ and gpIIb/IIIa with potential in the treatment of angiogenic disorders, inflammation, bone degradation, cancer, diabetic retinopathy, thrombosis, restenosis and macular degeneration. Other specifically claimed compounds include the following:



Compound	R1	X	Formula
281570	2,6-(NH ₂) ₂ -4-pyrimidinyl-CH ₂	CF ₃ CO ₂ H	C ₂₅ H ₃₀ N ₆ O ₅ S.C ₂ HF ₃ O ₂
281571	4-NH ₂ -2-quinazolinyl-NH		C ₂₈ H ₃₀ N ₆ O ₅ S



Compound	R1	X	Formula
281572	2,4,6-(Me) ₃ -PhSO ₂		C ₂₄ H ₂₈ N ₆ O ₅ S
281573	CO ₂ Bu	CF ₃ CO ₂ H	C ₂₀ H ₂₆ N ₆ O ₅ .C ₂ HF ₃ O ₂
281574	SO ₂ Ph	CF ₃ CO ₂ H	C ₂₁ H ₂₂ N ₆ O ₅ .C ₂ HF ₃ O ₂
281575	SO ₂ Bu	CF ₃ CO ₂ H	C ₁₉ H ₂₆ N ₆ O ₅ .C ₂ HF ₃ O ₂



281569: C₂₁ H₂₆ N₅ Na O₆

SOURCE – DuPont Pharmaceuticals.

REFERENCES

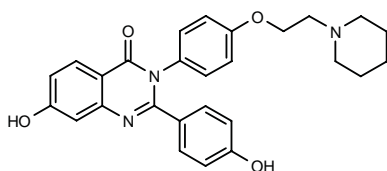
1. Pitts W.J. and Jadhav, P.K. (DuPont Pharmaceuticals Co.) *Integrin antagonists*. WO 9950249.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

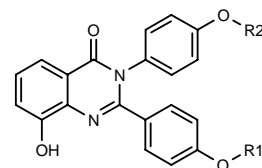
280442

7-Hydroxy-2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenyl]-4(3*H*)-quinazolinone



C₂₇ H₂₇ N₃ O₄; Mol wt: 457.5273

ACTION – Partial estrogen agonist with potential in the treatment of osteoporosis, prostatic hypertrophy and breast and endometrial cancer. Compound exhibited an IC₅₀ value of 6.5 μM for inhibition of [³H]-17β-estradiol binding to the human estrogen receptor expressed in CHO cells, as compared to values of 4.5 and 0.04 μM for tamoxifen and raloxifene, respectively. Compound exhibited antiestrogenic activity *in vitro* in the Ishikawa alkaline phosphatase assay and estrogenic activity in a luciferase assay using CHO cells transfected with the human estrogen receptor. Other specifically claimed compounds from this series of 2- or 3-(aminoalkoxyphenyl)-quinazolin-4-ones are:



Compound	R1	R2	Formula
280443	1-Pip-CH ₂ CH ₂	H	C ₂₇ H ₂₇ N ₃ O ₄
280444	H	1-Pip-CH ₂ CH ₂	C ₂₇ H ₂₇ N ₃ O ₄

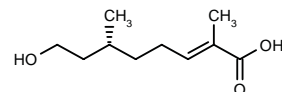
SOURCE – American Home Products.

REFERENCES

1. Koko, M.C. and Santilli, A.A. (American Home Products Corp.) *2- Or 3-(subst. aminoalkoxyphenyl)quinazolin-4-ones*. US 5948775.

280535

8-Hydroxy-2,6(*R*)-dimethyl-2(*E*)-octenoic acid



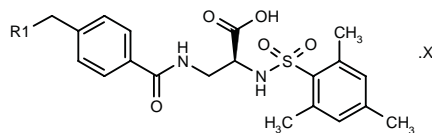
C₁₀ H₁₈ O₃; Mol wt: 186.2492

ACTION – Agent for the treatment of osteoporosis isolated from an extract of the plant *Cistanche salsa*, shown to inhibit the production of IL-6 *in vitro* (IC₅₀ = 27 μg/ml for inhibition of parathyroid hormone [PTH]-induced IL-6 secretion in murine osteoblast MC3T3-E1 cells). In ovariectomized mice, compound significantly suppressed bone weight loss induced by ovariectomy at 1.6-8 μg/kg/day i.p. x 4 weeks.

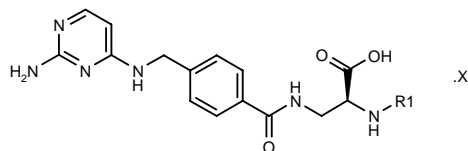
SOURCE – Sagami.

REFERENCES

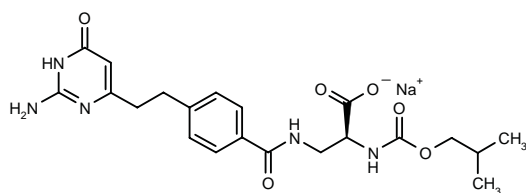
1. Yamaguchi, K. et al. (Sagami Chemical Research Center) *Anti-osteoporosis agents and (R)-8-hydroxy-2,6-dimethyl-2-octenoic acid*. JP 99209324.



Compound	R1	X	Formula
281570	2,6-(NH ₂) ₂ -4-pyrimidinyl-CH ₂	CF ₃ CO ₂ H	C ₂₅ H ₃₀ N ₆ O ₅ S.C ₂ HF ₃ O ₂
281571	4-NH ₂ -2-quinazolinyl-NH		C ₂₈ H ₃₀ N ₆ O ₅ S



Compound	R1	X	Formula
281572	2,4,6-(Me) ₃ -PhSO ₂		C ₂₄ H ₂₈ N ₆ O ₅ S
281573	CO ₂ Bu	CF ₃ CO ₂ H	C ₂₀ H ₂₆ N ₆ O ₅ .C ₂ HF ₃ O ₂
281574	SO ₂ Ph	CF ₃ CO ₂ H	C ₂₁ H ₂₂ N ₆ O ₅ .C ₂ HF ₃ O ₂
281575	SO ₂ Bu	CF ₃ CO ₂ H	C ₁₉ H ₂₆ N ₆ O ₅ .C ₂ HF ₃ O ₂



281569: C₂₁ H₂₆ N₅ Na O₆

SOURCE – DuPont Pharmaceuticals.

REFERENCES

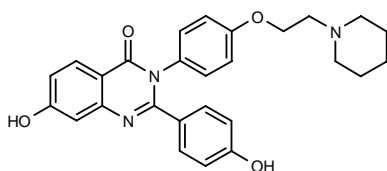
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

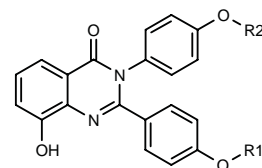
280442

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C₂₇ H₂₇ N₃ O₄; Mol wt: 457.5273

ACTION – Partial estrogen agonist with potential in the treatment of osteoporosis, prostatic hypertrophy and breast and endometrial cancer. Compound exhibited an IC₅₀ value of 6.5 μM for inhibition of [³H]-17β-estradiol binding to the human estrogen receptor expressed in CHO cells, as compared to values of 4.5 and 0.04 μM for tamoxifen and raloxifene, respectively. Compound exhibited antiestrogenic activity *in vitro* in the Ishikawa alkaline phosphatase assay and estrogenic activity in a luciferase assay using CHO cells transfected with the human estrogen receptor. Other specifically claimed compounds from this series of 2- or 3-(aminoalkoxyphenyl)-quinazolin-4-ones are:



Compound	R1	R2	Formula
280443	1-Pip-CH ₂ CH ₂	H	C ₂₇ H ₂₇ N ₃ O ₄
280444	H	1-Pip-CH ₂ CH ₂	C ₂₇ H ₂₇ N ₃ O ₄

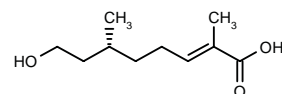
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280535

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ACTION – Agent for the treatment of osteoporosis isolated from an extract of the plant *Cistanche salsa*, shown to inhibit the production of IL-6 *in vitro* (IC₅₀ = 27 μg/ml for inhibition of parathyroid hormone [PTH]-induced IL-6 secretion in murine osteoblast MC3T3-E1 cells). In ovariectomized mice, compound significantly suppressed bone weight loss induced by ovariectomy at 1.6-8 μg/kg/day i.p. x 4 weeks.

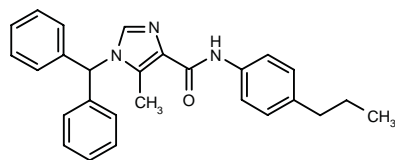
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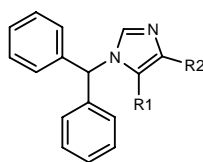
280542

1-(Diphenylmethyl)-5-methyl-*N*-(4-propylphenyl)-1*H*-imidazole-4-carboxamide



C27 H27 N3 O; Mol wt: 409.5303

ACTION – Agent for the treatment of osteoporosis shown to produce 86% inhibition of urinary hydroxyproline excretion in ovariectomized rats at 10 mg/kg/day p.o. x 2 weeks. Other nitrogen-containing heterocyclic compounds include the following:



Compound	R1	R2	Formula
280543	2-oxo-1-pyrrolidinyl- -(CH2)3NHCO	Me	C ₂₅ H ₂₈ N ₄ O ₂
280544	4-(2-Cl-Ph)-1-Piz-CO	Me	C ₂₈ H ₂₇ ClN ₄ O
280545	Me	4-(2-Cl-Ph)-1-Piz-CO	C ₂₈ H ₂₇ ClN ₄ O

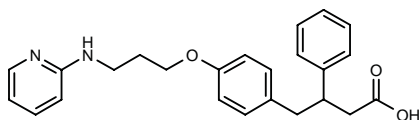
SOURCE – Kyowa Hakko.

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280941

3-Phenyl-4-[4-[3-(pyridin-2-ylamino)propoxy]phenyl]-butyric acid



C24 H26 N2 O3; Mol wt: 390.4804

ACTION – Agent for the treatment of osteoporosis, cancer, angiogenesis, atherosclerosis, restenosis and inflammation, a selective vitronectin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptor antagonist.

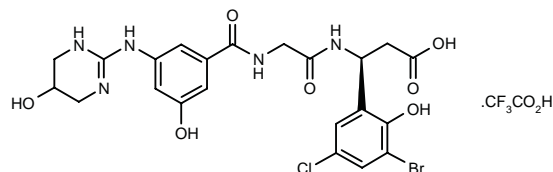
SOURCE – SmithKline Beecham.

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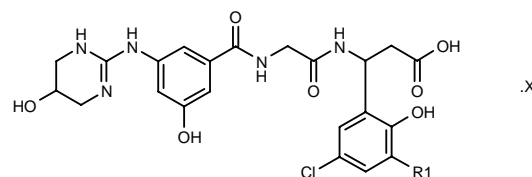
280962

3-(*S*)-(3-Bromo-5-chloro-2-hydroxyphenyl)-3-[2-[3-hydroxy-5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-yl-amino)benzamido]acetamido]propionic acid trifluoroacetate



C22 H23 Br Cl N5 O7 . C2 H F3 O2; Mol wt: 698.8306

ACTION – Potent integrin $\alpha_v\beta_3$ (vitronectin) receptor antagonist with high selectivity relative to the fibrinogen (gpIIb/IIIa) receptor (IC₅₀ = 0.37 and 388 nM, respectively, in human platelet-rich plasma). Potentially useful in the treatment of osteoporosis, hypercalcemia of malignancy, tumor growth and metastasis, angiogenesis, macular degeneration, rheumatoid arthritis, smooth muscle cell migration and restenosis. Other specifically claimed meta-azacyclic amino benzoic acid compounds include the following:



Compound	R1	Isomer	X	Formula
280963	Br		CF3CO2H	C ₂₂ H ₂₃ BrClN ₅ O ₇ ·C ₂ H ₃ F ₃ O ₂
280964	Cl			C ₂₂ H ₂₃ Cl ₂ N ₅ O ₇
280965	I			C ₂₂ H ₂₃ ClIN ₅ O ₇
280966	Cl	3S	.HCl.H2O	C ₂₂ H ₂₃ Cl ₂ N ₅ O ₇ ·HCl·H ₂ O

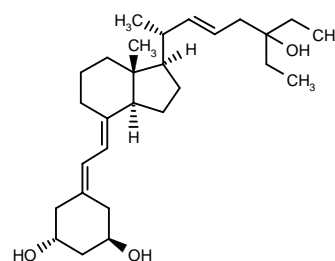
SOURCE – Searle.

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281329

22,23(*E*)-Didehydro-1 α ,25-dihydroxy-26,27-dimethyl-19-norvitamin D₃



C28 H46 O3; Mol wt: 430.6684

ACTION – Agent for the treatment of osteoporosis, a 19-nor-vitamin D₃ analogue with high binding affinity for the porcine intestinal vitamin D receptor and high potency in promoting the differentiation of HL-60 cells, being comparable to 1 α ,25-dihydroxyvitamin D₃. In addition, it shows a selective calcemic profile, being similar to 1,25-(OH)₂D₃ in inducing intestinal calcium transport and more active in inducing bone calcium mobilization. Compound proved extremely effective in increasing bone mass in a 12-month assay in ovariectomized rats, being clearly superior to 1,25-(OH)₂D₃.

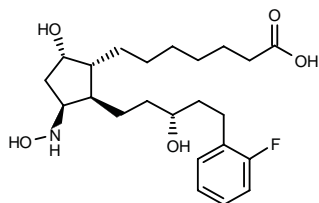
SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

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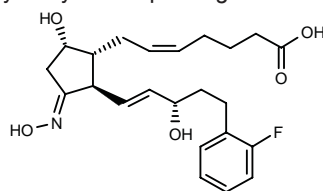
281446

11-Deoxo-17-(2-fluorophenyl)-11-(hydroxyimino)-18,19,20-trinorprostaglandin D₂



C23 H34 F N O5; Mol wt: 423.5216

ACTION – Prostaglandin analogue with potential in the treatment of bone disorders and glaucoma; compound is reported to possess advantages over existing bone therapies by virtue of its ability to increase trabecular number through formation of new trabeculae, increase bone mass and bone volume while maintaining a more normal bone turnover rate, as well as its ability to increase bone formation at the endosteal surface without increasing cortical porosity. Another compound from this series of C11 oxymyl and hydroxylamino prostaglandins is:



281447: C23 H30 F N O5

SOURCE – Procter & Gamble.

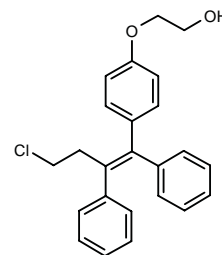
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TREATMENT OF LIPOPROTEIN DISORDERS

280358

2-[4-[4-Chloro-1,2-diphenylbut-1(E)-enyl]phenoxy]ethanol



C24 H23 Cl O2; Mol wt: 378.8967

ACTION – (E)-Isomer of a metabolite of the antiestrogen toremifene with comparable antiestrogenic activity but significantly more potent in lowering serum cholesterol, as demonstrated *in vitro* in HepG2 cells and *in vivo* in intact rats (57 vs. 45% decrease at 3.17 mg/kg/day p.o. x 2 weeks) and ovariectomized female rats (38 and 77% vs. 4 and 34% decrease, respectively, at 1 and 10 mg/kg/day p.o. x 2 weeks). Potentially useful in the treatment or prevention of hypercholesterolemia and atherosclerosis, as well as for use in hormone replacement therapy.

SOURCE – Orion Corporation.

REFERENCES

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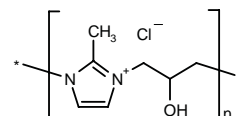
COLESTIMIDE*

185277

2-Methyl-1H-imidazole polymer with (chloromethyl oxirane)

2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane

Colestilan (Prop INN)
MCI-196⁺



(C7 H11 Cl N2 O)_n; Mol wt: 174.6299

White to pale yellowish powder.

ACTION – Bile acid sequestrant.

INDICATION – Treatment of hypercholesterolemia and familial hypercholesterolemia.

PRESENTATION – Tablets, 500 mg; granules, 70%.

PROPRIETARY NAME – Cholebine (JP).

SOURCES – Codeveloped by Mitsubishi Chemical and Tokyo Tanabe (now Mitsubishi-Tokyo Pharmaceuticals); comarketed by Yamanouchi.

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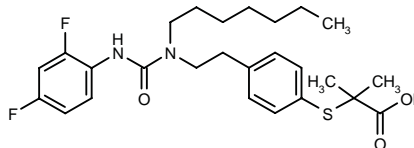
MONOGRAPH – Prous, J. and Castañer, J. *MCI-196*. Drugs Fut 1993, 18(1): 0015.

*Drug Data Rep 1992, 014(09): 0814.

GW-9578

280503

2-[4-[2-[3-(2,4-Difluorophenyl)-1-heptylureido]ethyl]-phenylsulfanyl]-2-methylpropionic acid



C26 H34 F2 N2 O3 S; Mol wt: 492.6276

ACTION – Potent human peroxisome proliferator-activated receptor PPAR α agonist (EC_{50} = 0.05 μ M) with excellent subtype selectivity over murine PPAR γ receptors (EC_{50} = 1.5 μ M) and moderate selectivity over human PPAR γ and PPAR δ receptors (EC_{50} = 1.0 and 0.2 μ M, respectively). In cholesterol/cholic acid-fed rats, compound was able to lower serum LDL cholesterol (minimum effective dose [MED] = 0.2 mg/kg/day p.o. for 3 days), and it also prevented body weight gain and the development of hyperinsulinemia in insulin-resistant rats. In comparison with standard serum cholesterol-lowering agents such as fenofibrate and bezafibrate, compound was 1000-fold more potent *in vitro* and much more effective *in vivo* in lowering LDL cholesterol. Potentially useful for the treatment of hyperlipidemia and for the prevention of coronary heart disease.

SOURCE – Glaxo Wellcome.

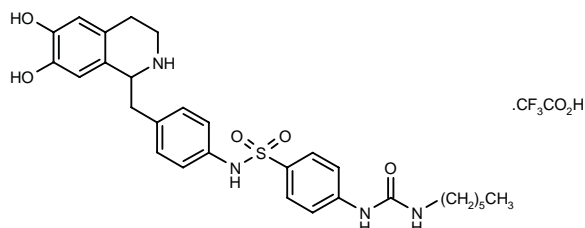
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

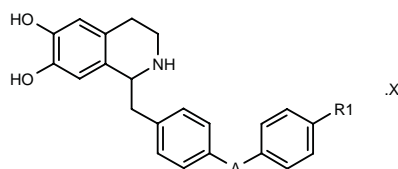
281130

N-[4-(6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)phenyl]-4-[3-hexylureido]benzenesulfonamide trifluoroacetate

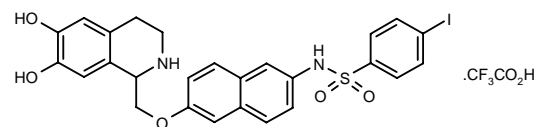


C29 H36 N4 O5 S . C2 H F3 O2; Mol wt: 666.7143

ACTION – Agent for the treatment of obesity and diabetes with selective β_3 -adrenoceptor-agonist activity and very little activity at β_1 - or β_2 -adrenoceptors. The compound can also be used to lower triglyceride and cholesterol levels, to increase HDL levels, to decrease gut motility and for the treatment of neurogenic inflammation or as an antidepressant. Other specifically claimed compounds from this series of fused piperidine substituted aryl-sulfonamides include the following:



Compound	R1	A	X	Formula
281132	6-(4-CF3-Ph)-2-pyrazinyl	-NHSO2-	CF3CO2H	C ₃₃ H ₂₇ F ₃ N ₄ O ₄ S .C ₂ HF ₃ O ₂
281133	4-(C ₆ H ₁₃ NHCONH)-PhSO2NH	bond	CF3CO2H	C ₃₈ H ₄₀ N ₄ O ₅ S .C ₂ HF ₃ O ₂
281134	NHSO2Me	bond		C ₂₃ H ₂₄ N ₂ O ₄ S



281136: C26 H23 I N2 O5 S . C2 H F3 O2

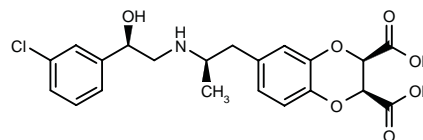
SOURCE – Merck & Co.

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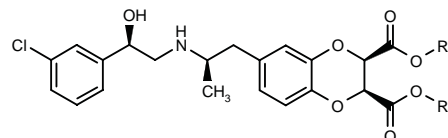
281541

cis-6-[2(R)-[2(R)-(3-Chlorophenyl)-2-hydroxyethyl-amino]propyl]-2,3-dihydro-1,4-benzodioxin-2,3-dicarboxylic acid



C21 H22 Cl N O7; Mol wt: 435.8578

ACTION – Selective β_3 -adrenoceptor agonist with potential in the treatment of diabetes, hyperglycemia and obesity. Within this series of substituted benzo[1,4]dioxin derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
281542	i-Pr	i-Pr	C ₂₇ H ₃₄ ClNO ₇
281543	i-Pr	H	C ₂₄ H ₂₈ ClNO ₇
281544	Bu	Bu	C ₂₉ H ₃₈ ClNO ₇
281545	CH ₂ CH ₂ OEt	CH ₂ CH ₂ OEt	C ₂₉ H ₃₈ ClNO ₉
281546	Et	Et	C ₂₆ H ₃₀ ClNO ₇
281547	cyclohexyl	cyclohexyl	C ₃₃ H ₄₂ ClNO ₇
281548	cyclopentyl	cyclopentyl	C ₃₁ H ₃₈ ClNO ₇
281549	C ₈ H ₁₇	C ₈ H ₁₇	C ₃₇ H ₅₄ ClNO ₇
281550	CH ₂ Ph	CH ₂ Ph	C ₃₅ H ₃₄ ClNO ₇

SOURCE – American Home Products.

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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

ERB1-7

281280

L-Aspartyl-L-arginyl-L-glutamyl-glycyl-L-cysteinyl-L-arginyl-L-arginyl-glycyl-L-tryptophyl-L-valyl-glycyl-L-glutamyl-L-cysteinyl-L-lysyl-L-alanyl-L-tryptophyl-L-phenylalanyl-L-asparagine

C93 H138 N32 O25 S2; Mol wt: 2168.4440

ACTION – Erythropoietin (EPO) peptidomimetic with affinity for the human EPO receptor, identified by a multistep procedure involving the creation of a chimeric receptor probe that binds EPO, the creation of a phage display library combined with mutagenesis techniques to generate subsequent mutagenesis libraries, the identification of lead clones followed by nucleic acid sequence determination and comparison to identify a consensus amino acid sequence and chemical synthesis of truncated peptides. Compound was shown to inhibit the binding of human EPO to a chimeric Ig-EPO receptor in an *in vitro* assay, as well as to concentration-dependently stimulate the proliferation of the EPO-responsive cell line TF-1. Another specifically claimed peptide is:

L-Aspartyl-L-valyl-L-glutamyl-L-alanyl-L-cysteinyl-glycyl-glycyl-glycyl-L-tryptophyl-L-valyl-glycyl-L-histidyl-L-cysteinyl-L-asparaginyl-L-tyrosyl-L-tryptophyl-L-leucyl-L-arginine

ERB1-8 [281281]

SOURCE – Chugai.

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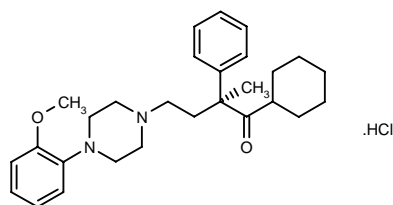
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TREATMENT OF POISONING AND DRUG DEPENDENCY

LY-426965*

277801

(+)-1-Cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-(S)-methyl-2-phenylbutan-1-one monohydrochloride



C28 H38 N2 O2 . HCl; Mol wt: 471.0811

ACTION – Potent 5-HT_{1A} receptor antagonist ($K_i = 4.66$ nM) with at least 20-fold selectivity over other 5-HT and non-5-HT receptor subtypes; it inhibited 5-HT-stimulated [³⁵S]-GTPγS binding to cloned human 5-HT_{1A} receptors ($K_i = 2.76$ nM) with full antagonist activity. In microdialysis studies compound (3 and 10 mg/kg p.o.) significantly potentiated the effect of fluoxetine on extracellular 5-HT content, and in electrophysiological studies it produced slight elevation of the firing rate of 5-HT neurons in dorsal raphe nucleus of rats. *In vivo*, compound blocked the 8-OH-DPAT-induced behavioral syndrome of lower lip retraction, flat body posture and hypothermia ($ED_{50} = 3.0, 2.0$ and 2.4 mg/kg p.o., respectively). It was also shown to antagonize the increase in serum corticosterone levels induced by 8-OH-DPAT ($ED_{50} = 9.2$ mg/kg p.o.), as well as to completely reverse the effects of nicotine withdrawal on the auditory startle reflex in rats ($ED_{50} = 0.1$ mg/kg p.o.). Potentially useful for the treatment of smoking cessation, anxiety, depression and related disorders.

SOURCES – Lilly; Synaptic.

REFERENCES

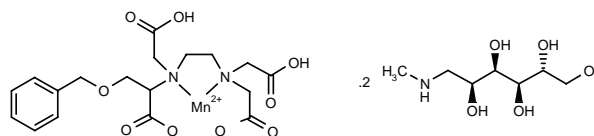
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*Identified compound 277801 Drug Data Rep 1999, 021(08): 0751.

DIAGNOSTIC AGENTS

280942

Dihydrogen [3-(benzyloxy)-2-[N-[2-[N,N-bis(carboxymethyl)amino]ethyl]-N-(carboxymethyl)amino]propanoate-(4-)]manganate(2-) compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)



C18 H22 Mn N2 O9 . 2 C7 H17 N O5; Mol wt: 855.7414

ACTION – Manganese chelate with high transversal relaxivity in human serum and good stability, for use in magnetic resonance imaging (MRI) of the liver, pancreas and gastrointestinal tract; due to its high relaxivity, it is also reported to be suitable for imaging the cardiovascular system.

SOURCES – Bracco; Dibra.

REFERENCES

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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

ERB1-7

281280

L-Aspartyl-L-arginyl-L-glutamyl-glycyl-L-cysteinyl-L-arginyl-L-arginyl-glycyl-L-tryptophyl-L-valyl-glycyl-L-glutamyl-L-cysteinyl-L-lysyl-L-alanyl-L-tryptophyl-L-phenylalanyl-L-asparagine

C93 H138 N32 O25 S2; Mol wt: 2168.4440

ACTION – Erythropoietin (EPO) peptidomimetic with affinity for the human EPO receptor, identified by a multistep procedure involving the creation of a chimeric receptor probe that binds EPO, the creation of a phage display library combined with mutagenesis techniques to generate subsequent mutagenesis libraries, the identification of lead clones followed by nucleic acid sequence determination and comparison to identify a consensus amino acid sequence and chemical synthesis of truncated peptides. Compound was shown to inhibit the binding of human EPO to a chimeric Ig-EPO receptor in an *in vitro* assay, as well as to concentration-dependently stimulate the proliferation of the EPO-responsive cell line TF-1. Another specifically claimed peptide is:

L-Aspartyl-L-valyl-L-glutamyl-L-alanyl-L-cysteinyl-glycyl-glycyl-glycyl-L-tryptophyl-L-valyl-glycyl-L-histidyl-L-cysteinyl-L-asparaginyl-L-tyrosyl-L-tryptophyl-L-leucyl-L-arginine

ERB1-8 [281281]

SOURCE – Chugai.

REFERENCES

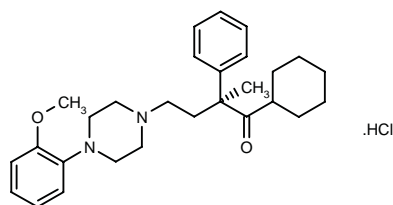
1. McConnell, S.J. and Spinella, D.G. (Chugai Pharmaceutical Co. Ltd.) *Peptide ligands for the erythropoietin receptor*. WO 947151.

TREATMENT OF POISONING AND DRUG DEPENDENCY

LY-426965*

277801

(+)-1-Cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-(S)-methyl-2-phenylbutan-1-one monohydrochloride



C28 H38 N2 O2 . HCl; Mol wt: 471.0811

ACTION – Potent 5-HT_{1A} receptor antagonist ($K_i = 4.66$ nM) with at least 20-fold selectivity over other 5-HT and non-5-HT receptor subtypes; it inhibited 5-HT-stimulated [³⁵S]-GTPγS binding to cloned human 5-HT_{1A} receptors ($K_i = 2.76$ nM) with full antagonist activity. In microdialysis studies compound (3 and 10 mg/kg p.o.) significantly potentiated the effect of fluoxetine on extracellular 5-HT content, and in electrophysiological studies it produced slight elevation of the firing rate of 5-HT neurons in dorsal raphe nucleus of rats. *In vivo*, compound blocked the 8-OH-DPAT-induced behavioral syndrome of lower lip retraction, flat body posture and hypothermia ($ED_{50} = 3.0, 2.0$ and 2.4 mg/kg p.o., respectively). It was also shown to antagonize the increase in serum corticosterone levels induced by 8-OH-DPAT ($ED_{50} = 9.2$ mg/kg p.o.), as well as to completely reverse the effects of nicotine withdrawal on the auditory startle reflex in rats ($ED_{50} = 0.1$ mg/kg p.o.). Potentially useful for the treatment of smoking cessation, anxiety, depression and related disorders.

SOURCES – Lilly; Synaptic.

REFERENCES

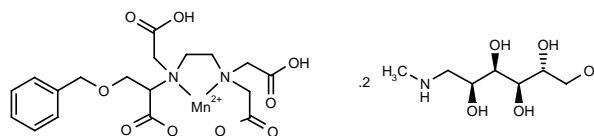
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*Identified compound 277801 Drug Data Rep 1999, 021(08): 0751.

DIAGNOSTIC AGENTS

280942

Dihydrogen [3-(benzyloxy)-2-[N-[2-[N,N-bis(carboxymethyl)amino]ethyl]-N-(carboxymethyl)amino]propanoate-(4-)]manganate(2-) compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)



C18 H22 Mn N2 O9 . 2 C7 H17 N O5; Mol wt: 855.7414

ACTION – Manganese chelate with high transversal relaxivity in human serum and good stability, for use in magnetic resonance imaging (MRI) of the liver, pancreas and gastrointestinal tract; due to its high relaxivity, it is also reported to be suitable for imaging the cardiovascular system.

SOURCES – Bracco; Dibra.

REFERENCES

1. Brocchetta, M. et al. (Bracco SpA; Dibra SpA) *Manganese chelates with high relaxivity in serum*. WO 9945968.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

ERB1-7

281280

L-Aspartyl-L-arginyl-L-glutamyl-glycyl-L-cysteinyl-L-arginyl-L-arginyl-glycyl-L-tryptophyl-L-valyl-glycyl-L-glutamyl-L-cysteinyl-L-lysyl-L-alanyl-L-tryptophyl-L-phenylalanyl-L-asparagine

C93 H138 N32 O25 S2; Mol wt: 2168.4440

ACTION – Erythropoietin (EPO) peptidomimetic with affinity for the human EPO receptor, identified by a multistep procedure involving the creation of a chimeric receptor probe that binds EPO, the creation of a phage display library combined with mutagenesis techniques to generate subsequent mutagenesis libraries, the identification of lead clones followed by nucleic acid sequence determination and comparison to identify a consensus amino acid sequence and chemical synthesis of truncated peptides. Compound was shown to inhibit the binding of human EPO to a chimeric Ig-EPO receptor in an *in vitro* assay, as well as to concentration-dependently stimulate the proliferation of the EPO-responsive cell line TF-1. Another specifically claimed peptide is:

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ERB1-8 [281281]

SOURCE – Chugai.

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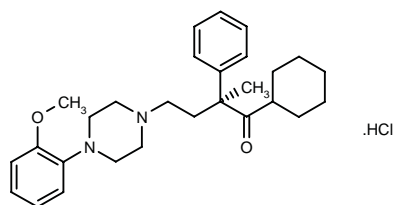
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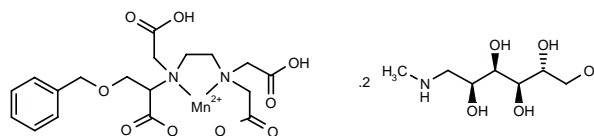
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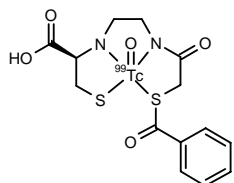
REFERENCES

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[^{99m}Tc]-L-CEMA

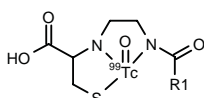
281108

Hydrogen [N-[2-[2-(benzoylsulfanyl)acetamido]ethyl]-L-cysteinato(4-)]oxotechnetate(1-)-⁹⁹Tc



C14 H15 N2 O5 S2 Tc; Mol wt: 454.4135

ACTION – Technetium chelate that is potentially useful as a radiodiagnostic compound for renal imaging and examination of renal function; it exhibits significantly superior renal clearance when compared to the reference agent ⁹⁹Tc-MAG3 in rats following i.v. injection. Other specifically claimed technetium chelates include the following:



Compound	R1	Isomer	Formula
[^{99m} Tc]-D-CEMA [281109]	CH2SCOPh	S	C ₁₄ H ₁₅ N ₂ O ₅ S ₂ Tc
[^{99m} Tc]-L-CEPIC [281110]	2-Pyr	R	C ₁₁ H ₁₂ N ₂ O ₄ STc

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

- Marzilli, L.G. et al. (Emory University) *Metal chelates as pharmaceutical imaging agents, processes of making such and uses thereof*. US 5955053.

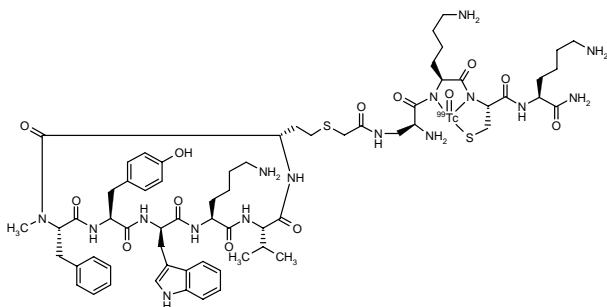
TECHNETIUM Tc 99m DEPREOTIDE

Prop INNM; USAN

217043

(SP-5-24)-[Cyclo(L-homocysteinyl-N-methyl-L-phenyl-alanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl) (1-1')-sulfide with 3-(2-mercaptoacetamido)-L-alanyl-L-lysyl-L-cysteinyl-L-lysynamidato(3-)]oxotechnetium-⁹⁹Tc

[^{99m}Tc]-P829



C65 H93 N16 O13 S2 Tc; Mol wt: 1469.6810

ACTION – Diagnostic radiopharmaceutical based on a synthetic peptide with high affinity for somatostatin receptors.

INDICATION – Scintigraphic imaging agent for identifying somatostatin receptor-bearing pulmonary masses in patients presenting with pulmonary lesions on computed tomography and or chest X-ray who have known malignancy or who are highly suspect for malignancy.

PRESENTATION – Kit for the preparation of technetium Tc 99m depreotide injection, vials containing 50 µg depreotide for reconstitution with sodium pertechnetate ^{99m}Tc injection in 0.9% sodium chloride injection.

PROPRIETARY NAME – *NeoTect* (US).

SOURCES – Diatide (now part of Schering AG); comarketed by Nycomed Amersham Imaging.

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23. *Data on Diatide diagnostics presented at Society of Nuclear Medicine meeting*. (Daily Essentials) 1999, June 14.

24. *Diatech files two investigational new drug applications including potential blockbuster for pulmonary embolism*. Diatech, Inc. Press Release 1995, Jan 5.

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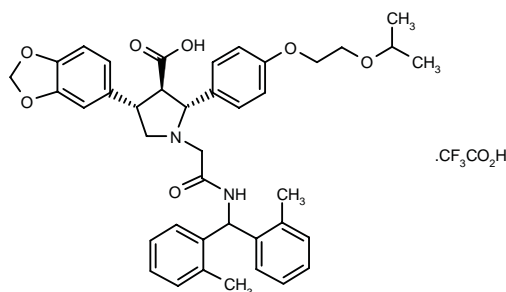
39. Hafslund Nycomed AS Annual Report 1995.

PHARMACOLOGICAL TOOLS

A-308165

279343

(2*R*,3*R*,4*S*)-4-(1,3-Benzodioxol-5-yl)-1-[2-[bis(2-methylphenyl)methylamino]-2-oxoethyl]-2-[4-(2-isopropoxyethoxy)phenyl]pyrrolidine-3-carboxylic acid trifluoroacetate



C40 H44 N2 O7 . C2 H F3 O2; Mol wt: 778.8165

White solid, $[\alpha]_D^{23} + 10.3^\circ$ (c 0.0016, MeOH).

ACTION – Potent human endothelin ET_B receptor antagonist ($IC_{50} = 1.9$ nM) with high selectivity over ET_A receptors ($IC_{50} = 51,703$ nM), with an acceptable pharmacokinetic profile in rats, i.e., good oral bioavailability (24%) and reasonable half-life (4.8 h) and total drug exposure. Potentially useful as a pharmacological tool for elucidating the role of ET_B receptors in both normal physiological and pathological conditions.

SOURCE – Abbott.

REFERENCES

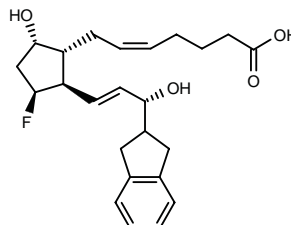
1. Liu, G. et al. *Design, synthesis, and activity of a series of pyrrolidine-3-carboxylic acid-based, highly specific, orally active ET_B antagonists containing a diphenylmethylamine acetamide side chain*. J Med Chem 1999, 42(18): 3679.

AL-8810

280308

7-[2(*R*)-[3(*R*)-(2,3-Dihydro-1*H*-inden-2-yl)-3-hydroxy-1(*E*)-propenyl]-3(*S*)-fluoro-5(*S*)-hydroxy-1(*R*)-cyclopentyl]-5(*Z*)-heptenoic acid

9(*S*),15(*R*)-Dihydroxy-11(*S*)-fluoro-15-(2-indanyl)-16,17,18,19,20-pentanor-5(*Z*),13(*E*)-prostadienoic acid



C24 H31 F O4; Mol wt: 402.5029

ACTION – Structural analogue of $PGF_{2\alpha}$ with selective partial agonist properties at the FP receptor, as demonstrated in rat thoracic aorta smooth muscle A7r5 cells ($EC_{50} = 261$ nM; $E_{max} = 19\%$) and in Swiss mouse 3T3 fibroblasts ($EC_{50} = 186$ nM; $E_{max} = 23\%$). Compound also exhibited properties of a competitive antagonist against the potent and selective FP receptor agonist fluprostenol ($pA_2 = 6.68$ and 6.34 , respectively, in A7r5 and 3T3 cells), and it antagonized the fluprostenol-induced activation of phospholipase C in HEK293 cells expressing cloned human ocular FP receptors, but did not significantly inhibit functional responses mediated by other prostaglandin receptor subtypes such as TP, DP, EP_2 and EP_4 in various cell lines at up to $10 \mu M$. Potentially useful as a pharmacological tool valuable for elucidating FP receptor-mediated functional responses in biological systems.

SOURCE – Alcon.

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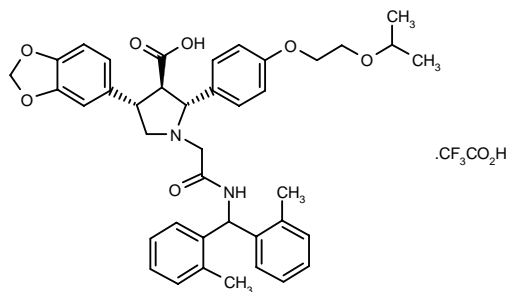
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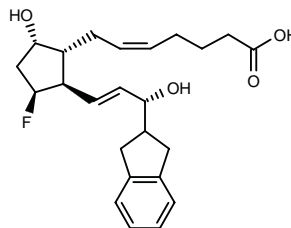
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C24 H31 F O4; Mol wt: 402.5029

ACTION – Structural analogue of $PGF_{2\alpha}$ with selective partial agonist properties at the FP receptor, as demonstrated in rat thoracic aorta smooth muscle A7r5 cells ($EC_{50} = 261$ nM; $E_{max} = 19\%$) and in Swiss mouse 3T3 fibroblasts ($EC_{50} = 186$ nM; $E_{max} = 23\%$). Compound also exhibited properties of a competitive antagonist against the potent and selective FP receptor agonist fluprostenol ($pA_2 = 6.68$ and 6.34 , respectively, in A7r5 and 3T3 cells), and it antagonized the fluprostenol-induced activation of phospholipase C in HEK293 cells expressing cloned human ocular FP receptors, but did not significantly inhibit functional responses mediated by other prostaglandin receptor subtypes such as TP, DP, EP_2 and EP_4 in various cell lines at up to $10 \mu M$. Potentially useful as a pharmacological tool valuable for elucidating FP receptor-mediated functional responses in biological systems.

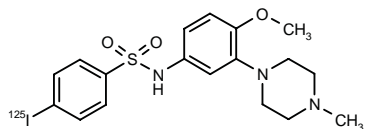
SOURCE – Alcon.

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[¹²⁵I]-SB-258585**279593**4-[¹²⁵I]Iodo-*N*-[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide

C18 H22 I N3 O3 S; Mol wt: 485.4558

ACTION – Potent and specific radioligand for 5-HT₆ receptors proven to label these receptors with high affinity both in stably transfected HeLa cells and in human caudate putamen membranes ($K_d = 0.8$ and 1.3 nM, respectively) and to have at least 100-fold selectivity over other 5-HT receptors. Its specific binding, which was 95% of total binding, was reversible. The high specific activity (2000 Ci/mmol) may allow binding studies on tissues with a low density of 5-HT₆ receptors and short-exposure autoradiographic studies.

SOURCE – SmithKline Beecham.**REFERENCES**

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